UNIVERSITY OF ALBERTA

Design and Synthesis of New Stannanes, Total Synthesis of Hamigeran B and Synthetic Studies on Halichlorine and Pinnaic Acid

by

Jian Wang ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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To my family

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LIST OF ABBREVIATIONS

Ac	acetyl
ACVA	4,4′-azobis(4-cyanovaleric acid)
AD	asymmetric dihydroxylation
AIBN	2,2′-azobisisobutyronitrile
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BTSE	1,2-bis(trimethylsilyloxy)ethane
Bu	butyl
t-Bu	*tert*-butyl
CAN	ammonium cerium(IV) nitrate
ca	about
Cf.	compare
CM	complex mixture
Cp	cyclopentadiene
Dba	*trans*,*trans*-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
Dess-Martin Reagent	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxo-

	3(1*H*)-one
DIBAL-H	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	ethylene glycol dimethyl ether
DMF	*N,N'*-dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
DP	desired product
Dppa	diphenylphosphoryl azide
Dppb	1,4-bis(diphenylphosphino)butane
Dppe	1,2-bis(diphenylphosphanyl)ethane
EDCI	*N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide
Et	ethyl
Fmoc	fluorenylmethoxycarbonyl
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoric triamide
HMQC	heteronuclear multiple quantum coherence
HOBT	hydroxybenzenetrizole
Hz	Hertz
KHMDS	potassium hexamethyldisilazide

LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LN	lithium naphthalenide
mCPBA	3-chloroperoxybenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
MeOH	methanol
Mes	2,4,6-trimethylphenyl
min	minute(s)
MOM	methoxymethoxymethyl
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
NR	no reaction
PCC	pyridinium chlorochromate
PDC	pyridinium
PG	protecting group
Ph	phenyl

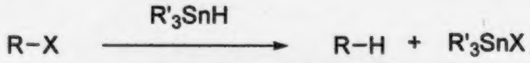
PPTSA	pyridinium *p*-toluenesulfonic acid
Pyr	pyridine
SET	single electron transfer
SM	starting material
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid

Chapter One

Design and Synthesis of New Stannanes

I Introduction

The use of radical reactions in organic synthesis has increased dramatically over the last twenty years. The combination of availability, stability, functional group compatibility, convenient hydrogen transfer rates to alkyl radicals, and excellent chain carrying properties of stannyl radicals have made tributyltin hydride (Bu_3SnH) and triphenyltin hydride[1] (Ph_3SnH) the most popular reagents in preparative free radical reactions such as dehalogenation,[2] deoxygenation[3] and radical cyclization.[4] Unfortunately, the tin-containing byproducts produced from these reactions, known as triorganotin halides or sulfides (Scheme 1), tend to hydrolyze slowly on silica gel, a property which sometimes makes column chromatographic separation and purification of the desired products difficult.[5] This problem is of special concern in the pharmaceutical industry because such impurities have to be reduced below trace levels to avoid toxicity.



X = halogen, OC(S)SMe *etc.*
R' = Ph or *n*-Bu

Scheme 1

Numerous approaches have been followed to remove tin-containing impurities from the products. Alternative reagents have also been devised to bypass the use of tin reagents. The following is a brief literature review of these approaches.

1.1 Development of various workup procedures for reactions involving stoichiometric tin hydride.

A number of workup procedures have been developed to remove tin-containing byproducts from reaction mixtures. Each method has potential disadvantages and the decision on which one to use often depends on the functional groups present in the products.

(1) Fluoride method.

This method was originally reported by Jacobus *et al.*[6]: organotin chlorides, bromides and iodides are all soluble in nonpolar organic solvents, but trialkyltin fluorides are penta-coordinated polymeric materials (e.g., the crystal structure of Me_3SnF consists of planar Me_3Sn units linked by interspersed fluorine) that are not soluble in common organic solvents or in water. Based on this fact, the desired separation of reduction products and organotin halides can be accomplished by conversion of the organotin halides to the insoluble organotin fluorides, which can then be separated readily by filtration.

Generally, the reaction mixture is taken up into Et_2O, treated with aqueous KF solution for a few hours, and then filtered through a Celite pad. This method is not suitable for compounds containing silicon protecting groups.

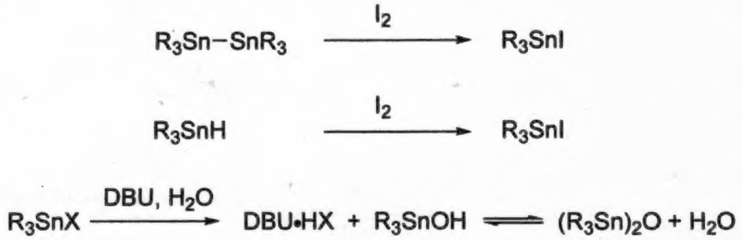
(2) Acetonitrile–hexane method.

Roberts and Berge[7] reported this method to solve the separation problem by partitioning the reaction mixture between hexane and acetonitrile. This procedure is based on the fact that hexane and acetonitrile are immiscible, and that organotin species have a pronounced solubility in hexane. The desired organic products are preferentially extracted into the acetonitrile layer.

Unfortunately, the partition of some organic compounds, especially those that are nonpolar, between these two solvents is not complete. Therefore, caution should be exercised in using this method with relatively nonpolar products and also in small-scale reactions.

(3) DBU method.

Curran and Chang[8] have developed this method, which relies on the reaction between DBU and an organotin halide in the presence of water. Generally, the reaction mixture from a tin-mediated radical reaction is diluted with reagent grade (undried) Et_2O and a slight excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is added. The excess of DBU is removed by addition of an ethereal solution of iodine until the iodine color just persists. Rapid filtration of this mixture through a short silica gel column, using Et_2O as eluent, leaves more than 90% of tin containing species on the column.



Scheme 2

As shown in Scheme 2, the addition of molecular iodine converts any hexaalkylditins and trialkyltin hydrides in the reaction mixture into trialkyltin iodides. In the presence of water, DBU hydrolyzes all tin halides to tin hydroxides with concomitant formation of DBU hydrohalides, which precipitate. The tin hydroxides are known to be in equilibrium with distannoxanes, and both these species are retained on silica gel with Et_2O as eluent, presumably due to rapid reaction with the free hydroxyl groups on the silica gel. This workup method requires that the products be insensitive to DBU and I_2.

(4) NH_3 method.

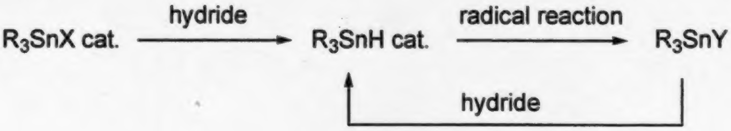
Davis and Johnson[9] reported this method to remove the trialkyltin halides from reaction products. Generally, the reaction mixture is diluted with Et_2O, cooled (ice-bath) and saturated with dry ammonia to precipitate the tin byproducts. This method is not suitable for base sensitive substrates.

(5) Reduction of tin halides.

Tin halides undergo hydrolysis on silica gel during chromatography, and separation from other compounds is often difficult. Unlike tin halides, tin hydrides (both Bu_3SnH and Ph_3SnH) have good chromatographic behavior and can often be separated chromatographically from reaction products. Based on this fact, Crich and Sun[10] suggested that the crude reaction mixture should be reduced with $NaCNBH_3$ so as to convert the tin species into separable tin hydrides. This treatment allows a good separation of non-polar tin hydrides from the reaction products in most cases. This method should not be used if the reaction products have reducible functionalities.

1.2 Use of catalytic tin hydride.

This method uses a catalytic amount of a tin hydride or its precursor, usually a tin halide, and stoichiometric amounts of another hydride, such as $LiAlH_4$,[11] $NaBH_4$,[12] $NaCNBH_3$,[13] polymethylhydrosiloxane,[14] or $PhSiH_3$.[15] During the reaction, a relatively small amount of tin hydride is constantly available for radical chain transfer by repeated regeneration from the reduction of the corresponding tin halide or sulfide (Scheme 3). Caution should be taken if the reaction products have reducible functionalities.

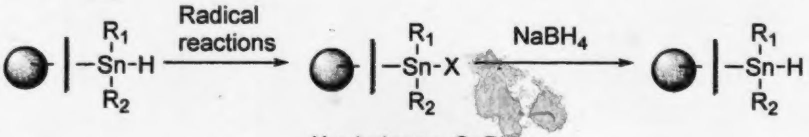


X, Y = halide, sulfide *etc.*

Scheme 3

1.3 Use of polymer-supported stannanes.

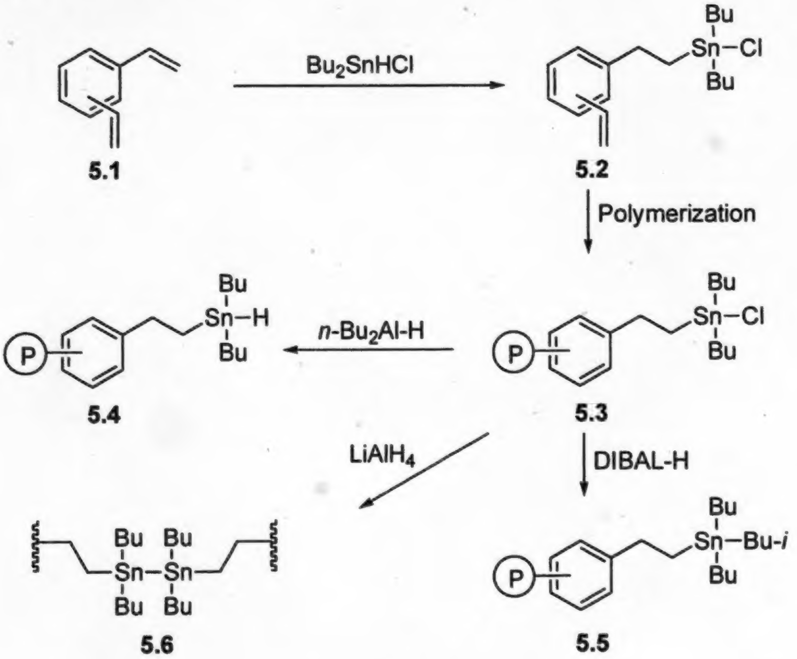
Polymer-supported tin hydrides would be expected to be the most effective reagents for isolating the desired organic compounds free from tin containing byproducts. The reaction products can be readily isolated from the polymeric tin halides by filtration because the polymers are insoluble in the reaction solvent. The solid polymeric tin halides can also be recycled to hydrides by reduction for further use (Scheme 4), although the recyclability is usually poor.



X = halogen, SePh

Scheme 4

One disadvantage of the solid-supported stannanes is that their preparation is not a simple task. Scheme 5 shows the preparation of a polymeric stannane developed by Neumann *et al.*[16]



Scheme 5

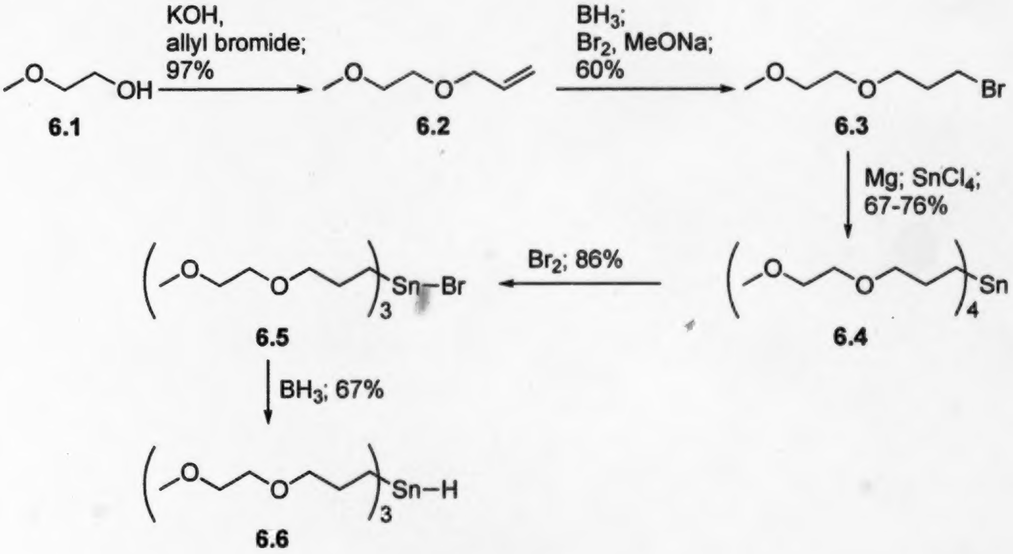
The tin-containing monomer **5.2** was easily synthesized by treatment of divinylbenzene with Bu_2SnHCl. Polymerization of **5.2** afforded polymer chloride **5.3**. A number of attempts at reduction of **5.3** showed that dibutylaluminum hydride is the best reagent for this process. The use of $LiAlH_4$ led to decomposition of the resulting tin hydride to distannane **5.6**; use of DIBAL-H led to substantial alkylation on tin to give compound **5.5**. Several radical dehalogenation reactions were conducted using the polymeric tin hydride **5.4**, with acceptable results, and it could be recycled after use at least five times without noticeable loss of activity.

1.4 Use of modified stannanes.

Instead of using the traditional reagents Bu_3SnH and Ph_3SnH, a number of alternative tin hydrides with modified alkyl chains have been designed to facilitate removal of organotin byproducts from reaction mixtures.

(1) Water-soluble modified stannanes.

Light and Breslow[17] first synthesized the water-soluble tin hydride **6.6**, which carries three methoxyethoxypropyl groups (Scheme 6).

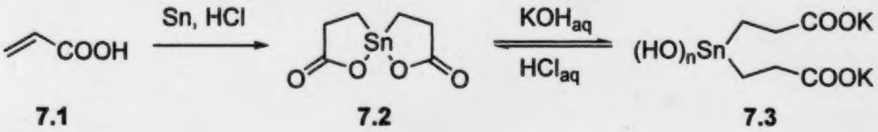


Scheme 6

This stannane could be used to conduct certain radical reactions in organic solvents such as PhH. In addition, its polar alkyl chains gave this stannane sufficient solubility in water (ca 30 mM at room temperature, more upon warming), so that it can reduce alkyl bromides and iodides in water, with 4,4'-azobis(4-cyanovaleric acid) (ACVA) or sunlamp initiation. Although it is not explicitly stated that this stannane leads to byproducts that are easily separated, the water solubility of the material and its polar nature would probably confer such characteristics.

The trialkyltin species resulting from reduction of bromides and iodides can be converted into corresponding tin chlorides simply by acidification with hydrochloric acid, and then extracted into $CHCl_3$. Evaporation of the solvent, followed by reduction with BH_3 in THF gives back stannane **6.6**.

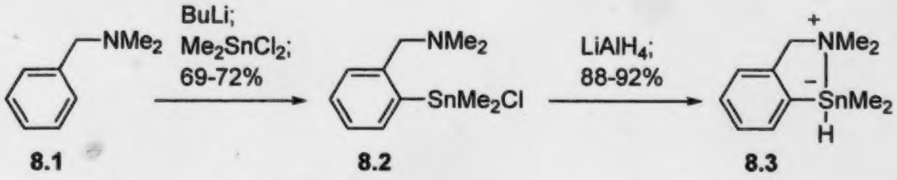
Similarly, Rai and Collum[18] reported their synthesis of an aqueous base-soluble polymeric tin species **7.2** (Scheme 7). Together with $NaBH_4$ and ACVA, this reagent was used to reduce a number of organic bromides, and for certain radical cyclizations. The reagent offers an alternative to the Breslow-Light stannane.



Scheme 7

(2) Nitrogen-containing stannanes.

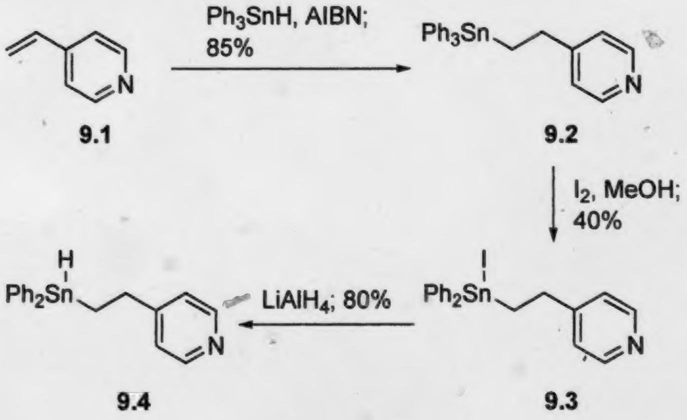
Vedejs *et al.*[19] published the synthesis of an internally activated tin hydride **8.3** (Scheme 8).



Scheme 8

The authors reported that this stannane could reduce ketones in a protic solvent such as methanol, and it could also serve as a radical reagent in an aprotic solvent such as PhH. The penta-coordinated nature of the tin, as shown in Scheme 8, could be the reason why this reagent has increased hydride donor reactivity. The tin halide byproducts from the reductions were crystalline and insoluble in Et_2O, and could be easily removed by filtration. However, the instability of compound **8.3** to heat limits its utility.

In our laboratory, a nitrogen containing stannane was also synthesized[20] (compound **9.4**, Scheme 9).

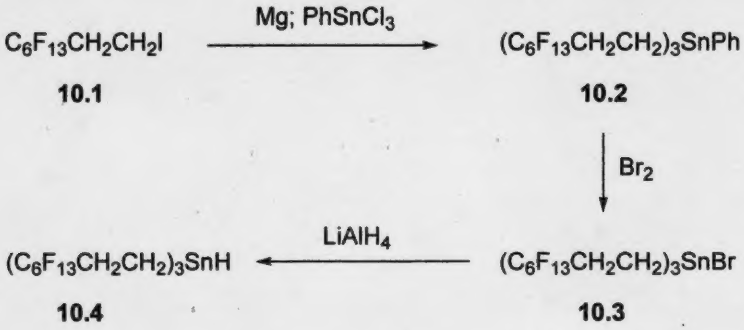


Scheme 9

Stannane **9.4** was tested in typical radical reactions for a number of organic bromides and selenides. Both yields and conditions were comparable to those with the traditional reagents Bu_3SnH and Ph_3SnH, but chromatographic separation is simplified in those cases where the desired product is non-polar, because of the high polarity of the stannane itself and its derivatives. Disappointingly, the stannane and its derivatives were not freely soluble in dilute hydrochloric acid.

(3) Fluorous tin hydrides.

Curran *et al.*[21] reported the synthesis and use of this new family of highly fluorinated tin hydrides. Based on the facts that fluorohydrocarbon solvents such as perfluoromethylcyclohexane (PFMC) are not miscible with common organic solvents or aqueous solutions, and that most highly fluorinated compounds are only soluble in perfluorohydrocarbon solvents, a number of special fluorous tin hydrides were synthesized and tested. One member of this group, stannane **10.4**, could be easily synthesized from 2-perfluorohexyl-1-iodoethane **10.1**, as shown in Scheme 10. This stannane was used in several typical radical reactions, with a lightly fluorinated solvent such as trifluoromethylbenzene, which can dissolve both fluoro compounds and regular hydrocarbons. After reaction, the trifluoromethylbenzene could be removed by evaporation and the residue was then partitioned between PFMC and CH_2Cl_2, with the desired product staying in the ordinary organic solvent and fluorous tin halides remaining in the PFMC.


$C_6F_{13}CH_2CH_2I$
10.1
Mg; $PhSnCl_3$
$(C_6F_{13}CH_2CH_2)_3SnPh$
10.2
Br_2
$(C_6F_{13}CH_2CH_2)_3SnBr$
10.3
$LiAlH_4$
$(C_6F_{13}CH_2CH_2)_3SnH$
10.4

Scheme 10

1.5 Use of alternatives to stannanes.

Many efforts have been made to seek replacements for traditional stannanes in radical reactions.[22]

(1) Organosilanes in radical reactions.[23]

Trialkylsilanes are poor reducing agents in free radical processes because the silicon-hydrogen bond is too strong for ready hydrogen transfer. Therefore chain processes are difficult to maintain under normal conditions and usually a higher reaction temperature (120-140 °C) is required. A way to avoid this problem is by adding a catalytic amount of an alkane thiol to the reaction mixture, because the nucleophilic alkyl radicals abstract hydrogen much more readily from thiols than from electron-rich trialkylsilanes, and the resulting electrophilic thiyl radicals abstract hydrogen more readily from silanes than do alkyl radicals; consequently, the chain processes are maintained (Scheme 11).

$$R^{\bullet} + R'SH \longrightarrow RH + R'S^{\bullet}$$

$$R'S^{\bullet} + R''_3SiH \longrightarrow R'SH + R''_3Si^{\bullet}$$

$$R''_3Si^{\bullet} + RX \longrightarrow R''_3SiX + R^{\bullet}$$

Scheme 11

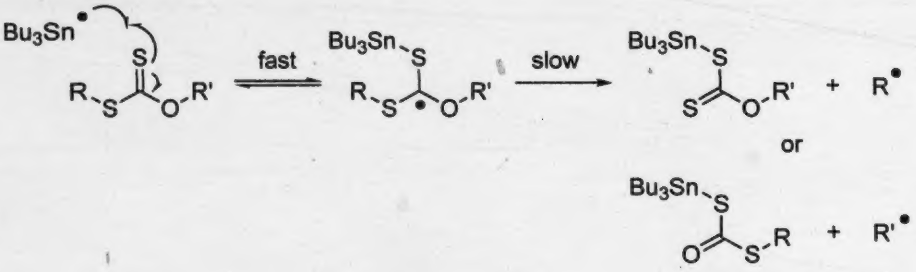
It was found that the silicon-hydrogen bond is dramatically weakened by successive substitution of silyl groups at the Si-H function. The most successful and widely used example, tris(trimethylsilyl)silane (TTMSS), has a Si-H bond that is only about 5 kcal·mol^{-1} stronger than the Sn-H bond of Bu_3SnH. This silicon reagent is a good hydrogen donor and is able to maintain radical chain processes. It can reduce a variety of organic functional groups with comparable yields to the tin hydride methods.

(2) Dialkyl phosphates and hypophosphorous acid.

Barton *et al.*[24] reported that reagents containing a P-H bond, such as dimethyl phosphite, diethyl phosphate, hypophosphorous acid [H_3PO_2, $H_2P(O)OH$] and various salts could be used as much cheaper, less toxic and easily removable radical reducing agents and chain carriers in the reduction of organic halides, thionoesters and isocyanides. These reactions were usually carried out with a radical initiator, such as benzoyl peroxide, in dioxane at reflux. For the reactions in aqueous solutions, a crystalline salt of hypophosphorous acid with a base (H_3PO_2.*N*-ethylpiperidine) was required to avoid acid-catalysed hydrolysis of water sensitive substrates. Oshima *et al.*[25] also reported their studies on this subject, in which various of organic halides were reduced efficiently by a combination of phosphinic acid, a base (e.g. $NaHCO_3$, KOH and Et_3N) and a radical initiator in aqueous ethanol at reflux. After the radical reaction, the excess reagents and phorphorus-containing byproducts could be easily removed from the reaction mixture by extraction.

(3) Gallium hydride.

Oshima *et al.*[26] reported that a gallium hydride ($HGaCl_2$) could be employed as a radical mediator – just like tin hydrides. A number of organic halides were reduced with this reagent in excellent yields, using Et_3B and air as initiator. Radical cyclization of halo acetals could also be done successfully with this reagent. In addition, use of only a catalytic amount of $GaCl_3$ along with an excess of Red-Al, which generates $HGaCl_2$ *in situ*, was also possible for the radical reactions.

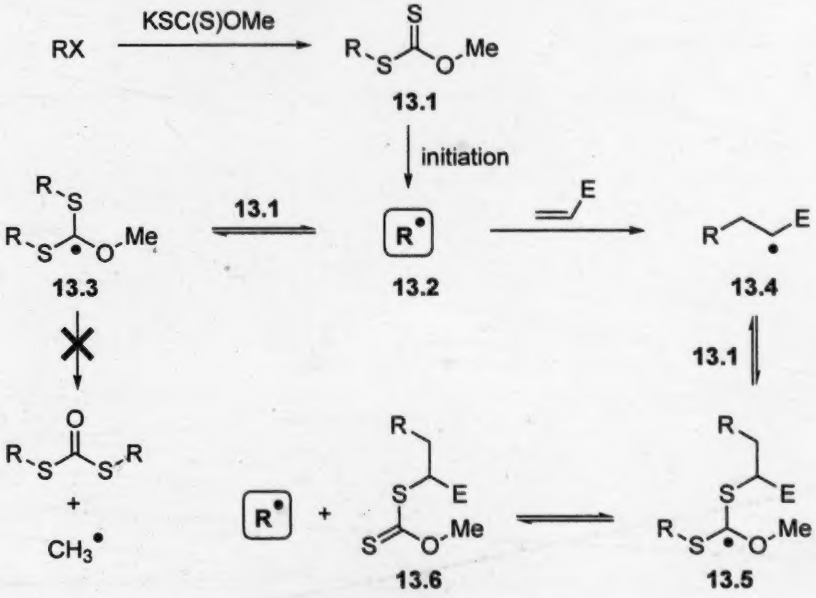


Scheme 12

(4) Xanthates as a new radical generating system.^{27}

During studies on the mechanism of the Barton-McCombie reaction,^{28} the Barton group concluded that the addition of the tin radical to the thiocarbonyl group is fast and reversible (Scheme 12), and the rate-determining step is β-scission of the carbon-oxygen or carbon-sulfur bond. The carbon-sulfur bond cleavage is more favored when radicals of similar stability are produced from both cleavages.

Based on this fact, xanthates of type **13.1** (Scheme 13), which were made by nucleophilic displacement of alkyl halides, tosylates, or methylsulfonates by potassium *O*-methyl xanthate, could be used in the radical-chain processes. As shown in Scheme 13, after the initiation step, only radical **13.2** could be generated by cleavage of the carbon-sulfur bond of xanthate **13.1**. This radical could react with starting xanthate to give radical **13.3**, which does not undergo carbon-oxygen cleavage because the resulting methyl radical is thermodynamically less stable than radical **13.2**. Rupture of either of the carbon-sulfur bonds in **13.3** affords radical **13.2** again and starting xanthate **13.1**. On the other hand, radical **13.2** could also be captured by a radical trap in the reaction medium, such as an olefin, to give radical **13.4**. This radical could then react with starting xanthate **13.1** to afford radical **13.5**, which undergoes another reversible step to provide a new xanthate **13.6** and to regenerate radical **13.2** as the chain carrier. In this process, a new carbon-carbon and a new carbon-sulfur bond are created. One limitation of this process is that the last two steps (**13.4** → **13.6**) are reversible, so that radical **13.4** should be more stable than radical **13.2** in order to avoid the reverse reaction.

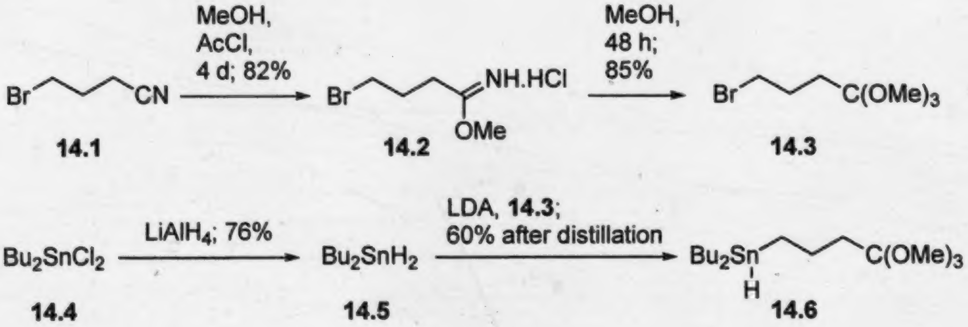


Scheme 13

II Results and Discussion

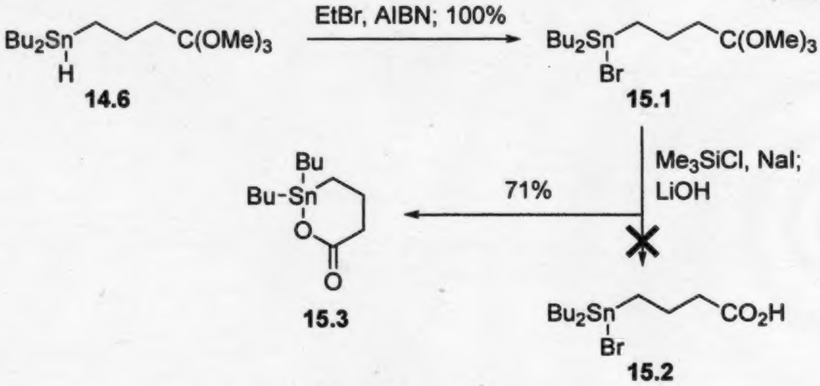
In connection with some free radical experiments done in this laboratory, a need was developed for a readily accessible stannane, $R_1R_2R_3SnH$, whose derivatives, $R_1R_2R_3SnX$ (X = halogen or SePh) could be converted by acid or base treatment under mild conditions into a carboxylic acid that is soluble in aqueous $NaHCO_3$.

Our first aim was to make stannane **14.6** (Scheme 14), which bears an orthoester side chain. The synthesis of this stannane is summarized in Scheme 14. The required alkyl bromide **14.3** was made from 4-bromobutanenitrile (**14.1**) by the literature procedure[29] in high yield (**14.1** → **14.2** → **14.3**, Scheme 14). Dibutyltin dihydride (**14.5**), freshly made by $LiAlH_4$ reduction of Bu_2SnCl_2,[30] was first deprotonated with 1 equiv of LDA,[31] and then alkylated with **14.3** to afford stannane **14.6** in 60% yield after ultra-high vacuum distillation (bp 120-125 °C, 0.003 mmHg).



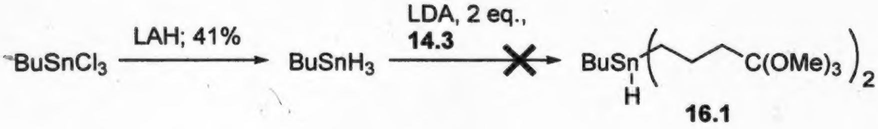
Scheme 14

Stannane **14.6** is a thick colorless oil which decomposed on either silica gel or Grade III alumina. To see if this tin hydride had the desired features, we used it in the reduction of bromoethane under standard radical conditions, and we were able to separate the tin bromide **15.1** quantitatively (Scheme 15). However, after we treated this compound with Me$_3$SiI and then LiOH, we did not obtain the expected acid **15.2**; only the cyclized compound **15.3** was isolated (71% yield).



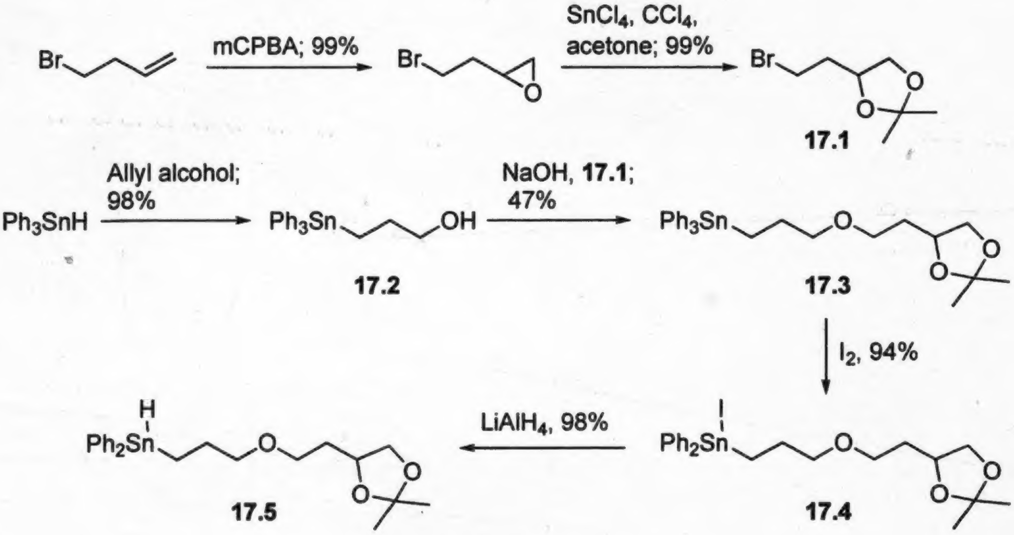
Scheme 15

Because of the unexpected replacement of tin-bound halide by the oxygen on the polar alkyl chain, we decided to make a tin hydride with two polar sites, such as stannane **16.1** (Scheme 16), so that we would have at least one site left after possible cyclization. To this end, BuSnH$_3$, freshly made by LiAlH$_4$ reduction of BuSnCl$_3$[30] (41% after distillation), was treated with 2 equiv of LDA and then with an excess of bromide **14.3**. However, we were unable to obtain any pure **16.1** after ultra high vacuum distillation. We did not establish whether this stannane was not generated from the above experiment or whether the desired stannane actually decomposed upon heating before it distilled.



Scheme 16

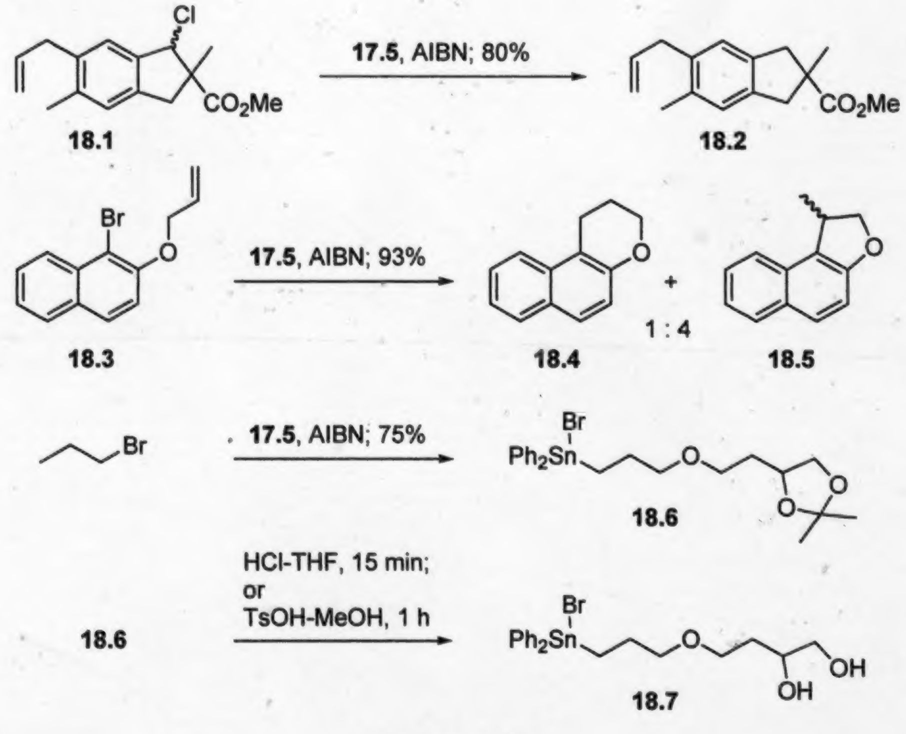
We felt that making stannanes with two polar alkyl chains would be rather difficult, and so we decided to concentrate on stannanes having a *single* alkyl chain which would bear two or more polar functionalities. Based on this decision, we first made stannane **17.5** (Scheme 17).



Scheme 17

As shown in Scheme 17, the bromide unit **17.1** was easily made in excellent yield from 4-bromobutene by epoxidation and then direct ketal formation from the epoxide.[32] Ph_3SnH, freshly made from Ph_3SnCl,[33] was used for hydrostannylation of allyl alcohol to afford compound **17.2**. Nucleophilic displacement by this alcohol on bromide **17.1** furnished the stannane **17.3** (50% aqueous NaOH, 47%). One of the phenyl groups was then replaced by treatment with 1 equiv of I_2[34] to give iodide **17.4**. Reduction of **17.4** with $LiAlH_4$ gave stannane **17.5** in 98% yield after aqueous workup.

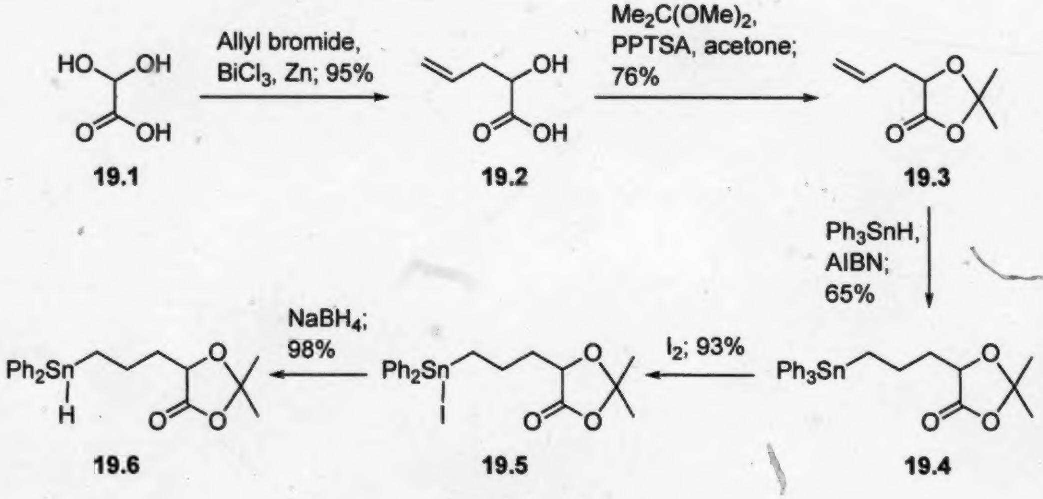
We carried out a few reductions and a radical cyclization with stannane **17.5**, under standard radical reaction conditions, and the results were very satisfactory (Scheme 18).



Scheme 18

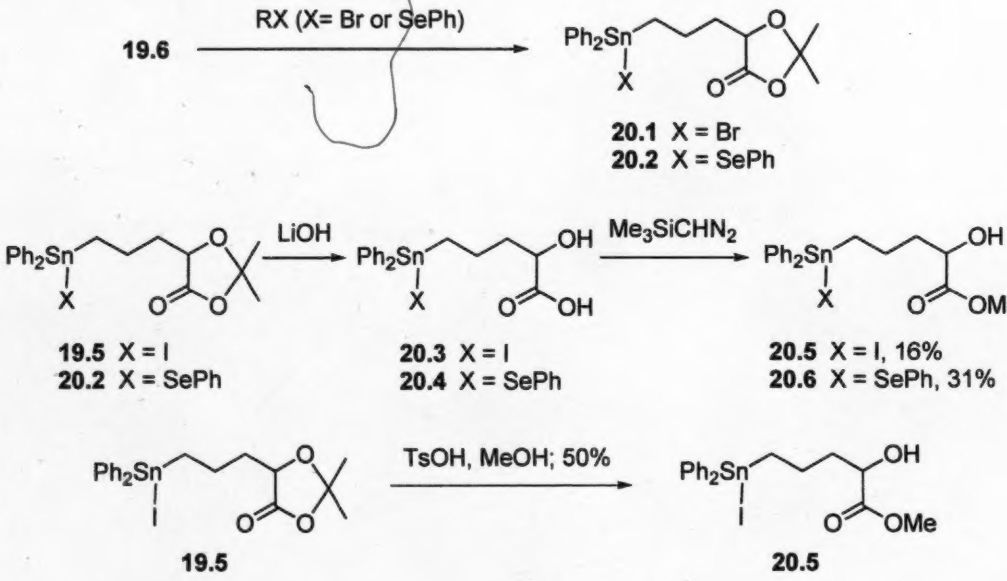
To see if this new stannane led to easily removable tin species, we also collected the tin bromide **18.6** after the reduction of 1-bromopropane (75%, Scheme 18). Treatment of compound **18.6** with either aqueous HCl (3%) in THF for 15 min or TsOH in MeOH for 1 h did indeed hydrolyze the ketal unit to give diol **18.7**. Both compound **18.6** and **18.7** are polar substances (e.g. for compound **18.6**, one needs 1:4 EtOAc-hexane for an R_f of 0.2 to 0.3 on silica gel plates), and so they could usually be easily separated from the reaction products by a single flash chromatography.

Although stannane **17.5** could serve as a polar tin hydride in radical reactions and the tin residues could be easily removed by flash chromatography, it still did not satisfy our objectives because the hydrolyzed product **18.7** is not water-soluble. After some further exploratory work, we settled on stannane **19.6** (Scheme 19), which matched all our requirements.



Scheme 19

The synthesis of the new stannane **19.6** is shown in Scheme 19. The known hydroxy acid **19.2** was easily prepared in 95% yield by a literature procedure[35] that calls for treatment of glyoxylic acid hydrate (**19.1**) with $BiCl_3$, Zn and allyl bromide. Ketalization under standard conditions (2,2-dimethoxypropane, TsOH·pyridine, acetone) gave the derived ketal **19.3** in 76% yield. When this was heated with an excess (1.5 equiv) of freshly prepared Ph_3SnH in PhH, in the presence of a catalytic amount of AIBN, the hydrostannylated product **19.4** could be isolated in 65% yield. Treatment of compound **19.4** with 1 equiv of I_2[34] again served to replace one of the phenyl groups by I (**19.4** → **19.5**), and then reduction with $NaBH_4$ gave the required stannane **19.6** (98%) as a colorless oil, which was obtained pure by rapid flash chromatography over silica gel. We stored this stannane under Ar in a refrigerator; the material was stable for at least two months under these conditions and was still reactive even after 2 years of storage (and was used by other members of this laboratory).



Scheme 20

To establish the properties of the anticipated tin containing reaction products, the tin bromide **20.1** and the tin selenide **20.2** were also prepared (Scheme 20). The former was prepared by reaction of stannane **19.6** with 1-bromopropane under standard conditions (see Experimental Section), and the latter by reaction of **19.6** with selenide **21.6** (see Table 1, entry 11). Compounds **19.5** and **20.2** (we did not examine **20.1**) were stirred in an aqueous THF solution of LiOH (ca 10 equiv) for several hours, and the presumed acid products **20.3** and **20.4**, obtained by acidification, were then esterified with Me_3SiCHN_2 to give esters **20.5** (16%) and **20.6** (31%), respectively. Compound **19.5** was also hydrolyzed under acidic conditions ($TsOH{\cdot}H_2O$) in MeOH, to give **20.5** (50%) directly.

We have evaluated the performance of stannane **19.6** by using it in typical radical reactions, as summarized in Table 1. The Table shows reduction of bromides (entries 1-4), a benzylic chloride (entry 5), and selenides (entries 6 and 7), radical cyclization onto a carbon-carbon double bond (entries 9, 10, 11, and 16), radical cyclization onto a triple bond (entries 12 and 13), stannane addition to a triple bond, followed by cyclization of the resulting vinyl radical and subsequent protodestannylation (entry 14), and cyclization onto an oxime (entry 15). Entry 8 shows an example of Barton-McCombie deoxygenation.

The reactions with stannane **19.6** could be initiated by AIBN in PhH or PhMe at reflux, or by Et_3B and air at room temperature. In all cases, except those of entries 1 (procedure giving 85% yield), 7, 15 and 16, the crude reaction mixture was stirred with a solution of LiOH in aqueous THF for 1.5-3 h (TLC control), and the organic-soluble product was purified by flash chromatography. For reduction of **21.1** (entry 1) we also tried acidic workup, the crude reaction mixture in this case being stirred with an aqueous THF solution of TsOH. The product **21.2** was then isolated in 85% yield.

Table 1

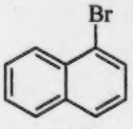
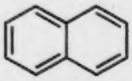
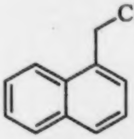
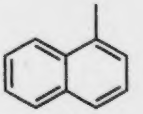
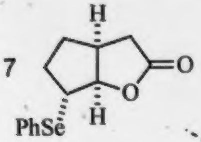
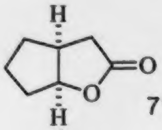
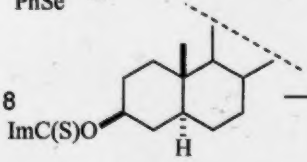
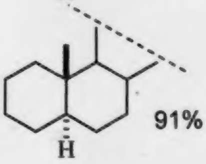
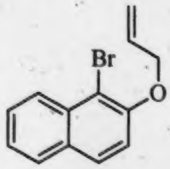
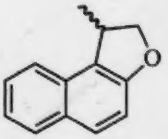
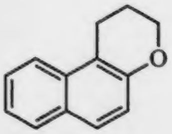
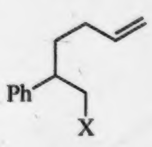
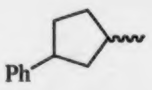
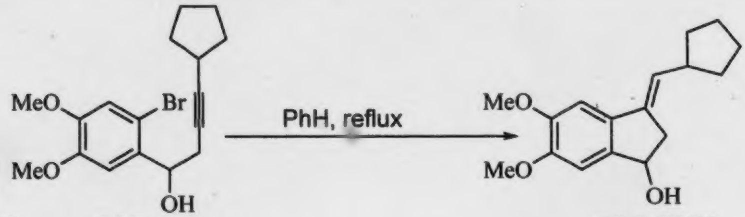
1	n-$C_{12}H_{25}Br$ **21.1**	PhMe, reflux	n-$C_{12}H_{26}$ **21.2** 91%, 85%[a]
2	**21.1**	PhMe, Et_3B, air[b]	**21.2** 93%
3	 **21.3**	PhH, reflux	 **21.4** 86%
4	**21.3**	PhH, Et_3B, air[b]	**21.4** 81%
5		PhH, reflux	 92%
6	n-$C_{12}H_{25}SePh$	PhMe, reflux	n-$C_{12}H_{26}$ 82%
7		PhMe, reflux	 71%[a]
8		PhMe, reflux	 91%
9	 **18.3**	PhH, reflux	 **18.5** 63%  **18.4** 31%
10	 **21.5** X = I	PhMe, reflux	 **21.7** 83%
11	**21.6** X = SePh	PhMe, reflux	**21.7** 74%

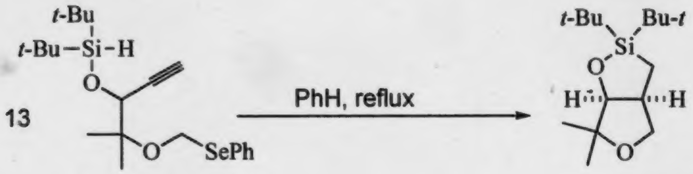
Table 1 (Continued)

12



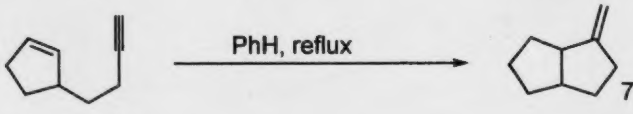
21.8 **21.9** 90%[c]

13



21.10 **21.11** 78%

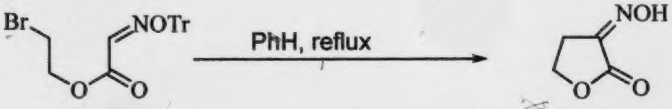
14



70%[d]

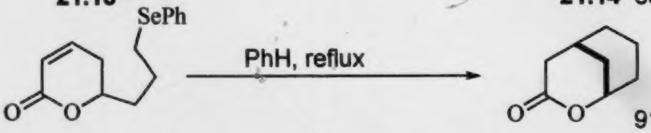
21.12

15



21.13 **21.14** 88%[a]

16



91%[a]

Reaction conditions, unless indicated otherwise: **19.6**, AIBN, PhH or PhMe, relfux. Workup, unless indicated otherewise: LiOH, water-THF, extract with Et_2O, wash with $NaHCO_3$, flash chromatography.

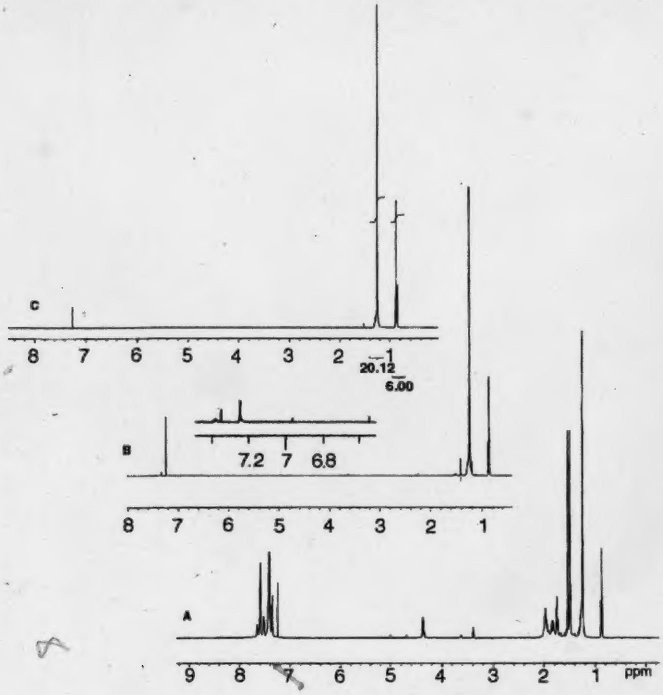
[a] Workup: $TsOH.H_2O$, aqueous THF, extract with Et_2O, wash with $NaHCO_3$, flash chromatography.

[b] Room temperature.

[c] A single isomer of unestablished geometry.

[d] The initial radical cyclization product was treated with CF_3CO_2H before LiOH.

In one case (entry 2), the ^1H NMR spectrum of the organic-soluble product was measured before and after flash chromatography. In two cases (entries 1 and 6) the same two measurements were again made, but in addition, the ^1H NMR spectrum was run before workup. The three spectra for entry 1 (91% yield) are shown in Figure 1. These spectra establish that the LiOH treatment removes all but traces of aryl-containing species, but leaves slight impurities (signals at δ 1.4, 1.5, and 3.6). All these impurities are removed by flash chromatography (in this case, using hexane as eluent). When acidic workup was used after reduction of **21.1** (entry 1, 85% yield), the three corresponding ^1H NMR spectra were very similar to those shown in Figure 1.



Trace A: ^1H NMR spectrum measured after evaporation of reaction solvent for entry 1 of Table 1.

Trace B: ^1H NMR spectrum measured after LiOH treatment. Inset: expansion (ca 4 x) of region δ 6.5-7.4. The chloroform signal is truncated.

Trace C: ^1H NMR spectrum measured after chromatography.

Figure 1

While most of the experiments listed in Table 1 gave products that are stable to mild base (LiOH and $NaHCO_3$), for the examples of entries 7, 15, and 16 we used acidic conditions for workup, followed by extraction of the tin species into saturated aqueous $NaHCO_3$.

Conclusion

We have designed and synthesized three new stannane reagents, which are suitable as replacements for traditional tin hydrides. Among our new compounds, stannane **19.6** behaves similarly to the standard Bu_3SnH and Ph_3SnH, with the additional characteristic that the tin containing by-products are easily removed. This substance is clearly our preferred stannane for radical reactions that would otherwise give products that are difficult to separate from tin residues.

III Experimental Section

General procedure

Unless stated to the contrary, reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311[36] catalyst and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and EtOAc used for chromatography were distilled before use. t-BuOMe was used directly from the bottle.

Products were isolated from solution by concentration under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Cannula transfers were done by supplying Ar under slight pressure to the flask containing the solution to be transferred.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by examination under UV light, or by spraying the plate with a solution of phosphomolybdic acid followed by charring with a heat gun. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, PhH, PhMe, dioxane and Et_2O were distilled from sodium and benzophenone ketyl. CH_2Cl_2, acetonitrile, DMF, and pyridine were stirred overnight with crushed CaH_2, and then distilled (under water pump vacuum in the case of DMF), with protection from moisture.

FTIR measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s, d, t, and q used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. In cases where the number of signals is less than expected, we assume this is due to coincident chemical shifts.

Known reaction products were identified by comparison of their NMR spectra (usually both ^{1}H NMR and ^{13}C NMR) with reported values.

General procedures for radical reaction and workup

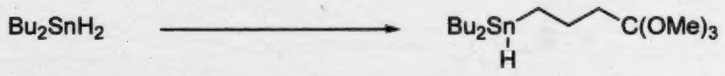
(a) Thermal radical reactions

The substrate (0.2 mmol) was placed in a dry round-bottomed flask carrying a reflux condenser closed by a septum. The flask was flushed with Ar, and the contents were kept under a slight positive pressure of Ar. PhH or PhMe (3 mL) was injected, and the flask was lowered into a preheated oil bath at 85 °C, or at 125 °C in the case of PhMe. A solution of both stannane **19.6** (0.28 mmol, 1.4 equiv) and AIBN (1 mg) in the same solvent (3 mL plus 1 mL as a rinse) was injected in one portion (except for the radical cyclizations, in which case the addition was made over 6 h). In the case of slow addition, care was taken to make sure that the tip of the syringe needle rested in a cold part of the reflux condenser. Refluxing was continued for 2-10 h after the addition. The mixture was cooled and concentrated. Aqueous LiOH (1.0 M, 2 mL) in THF (2 mL) or aqueous TsOH (0.25 M, 2 mL) in THF (2 mL) was added to the residue, and the mixture was stirred at room temperature for 1.5-3 h (TLC control). After all the tin dioxolanone had been hydrolyzed, Et_2O (20 mL) was added, the organic layer was washed with saturated aqueous $NaHCO_3$ (3 x 20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel then gave the product.

(b) Room temperature radical reactions

Stannane **19.6** (1.4 mmol) in PhH (4 mL) and Et_3B (1.0 M in hexane, 1.1 mL, 1.1 mmol) were added to a stirred solution of the substrate (1.0 mmol) in hexane (5 mL) contained in a flask fitted with a calcium sulfate guard tube. The mixture was stirred for 11 h with exposure to air (via the guard tube), and the same work-up procedure was followed as for the thermal method.

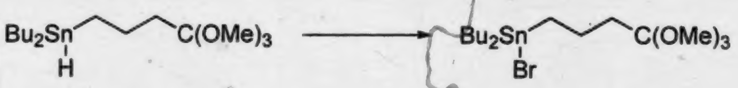
Dibutyl(4,4,4-trimethoxybutyl)stannane (14.6).



14.5 **14.6**

n-BuLi (2.5 M in hexane, 6.4 mL, 16.0 mmol) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (2.7 mL, 19.0 mmol) in THF (20 mL). After 15 min, a solution of freshly prepared Bu_2SnH_2 (4.13 g, 17.6 mmol) in THF (10 mL) was added dropwise over ca. 15 min. Stirring at -78 °C was continued for 30 min and a solution of 4-bromo-1,1,1-trimethoxybutane (**14.3**) (3.60 g, 15.9 mmol) in THF (10 mL) was added dropwise over ca. 15 min. The cold bath was left in place but not recharged and stirring was continued for 6 h. The reaction mixture was quenched by the addition of water (50 mL) and then extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Ultra high vacuum (0.003 mmHg) distillation of the residue, gave stannane **14.6** (fraction bp 120-125 °C, 3.68 g, 61%) as a colorless oil: ^1H NMR (C_6D_6, 400 MHz) δ 0.90-1.05 (m, 12 H), 1.30-1.43 (m, 4 H), 1.50-1.70 (m, 4 H), 1.80-1.90 (m, 4 H), 3.20 (s, 9 H), 5.09-5.13 (m, 1 H); ^{13}C NMR (C_6D_6, 50.3 MHz) δ 8.1 (t), 8.3 (t), 13.6 (q), 21.5 (t), 27.1 (t), 29.9 (t), 35.7 (t), 49.0 (q), 115.3 (s); exact mass *m/z* calcd for $C_{13}H_{27}O^{120}Sn$ (M - $C_2H_7O_2$) 319.1084, found 319.1083.

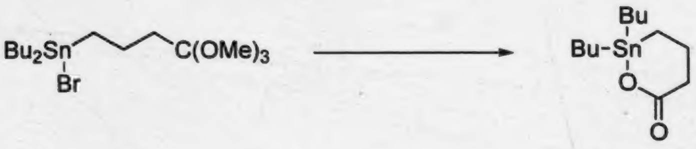
Bromodibutyl(4,4,4-trimethoxybutyl)stannane (15.1).



14.6 **15.1**

1-Bromopropane (0.33 g, 2.7 mmol) was added in one portion to a stirred solution of stannane **14.6** (0.62 g, 1.4 mmol) and AIBN (9 mg) in PhH (10 mL). The mixture was heated at reflux (85 °C) for 5 h and then cooled to room temperature. Evaporation of the solvent gave bromide **15.1** (0.71 g, 94%) as a colorless oil: ^1H NMR (C_6D_6, 400 MHz) δ 0.90-1.05 (m, 6 H), 1.20-1.98 (m, 18 H), 3.10 (s, 9 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 13.5 (q), 17.1 (t), 17.8 (t), 20.0 (t), 26.8 (t), 28.3 (t), 34.6 (t), 49.1 (q), 115.3 (s).

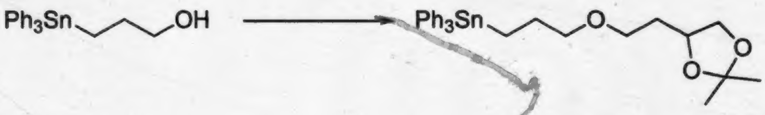
2,2-Dibutyl-1,2-oxastanninan-6-one (15.3).



15.1 **15.3**

NaI (1.14 g, 7.6 mmol) was added in one portion to a stirred solution of stannane **15.1** (1.17 g, 2.5 mmol) in MeCN (30 mL). Stirring was continued for 5 min and then Me_3SiCl (0.96 mL, 7.6 mmol) was added dropwise over ca. 5 min. Stirring was continued for 3 h at room temperature. The reaction mixture was diluted with Et_2O (50 mL) and washed with water (30 mL), saturated aqueous $Na_2S_2O_3$ (30 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine, dried ($MgSO_4$) and concentrated. Aqueous LiOH (1.0 M, 20 mL) was added to a stirred solution of the residue in THF (20 mL). Stirring was continued for 1 h and the reaction mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with water and brine, dried and concentrated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:4 EtOAc-hexane, gave compound **15.3** (0.54 g, 71%) as a colorless oil: FTIR ($CHCl_3$ cast) 2954, 1541, 1431 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 8.0 Hz, 6 H), 1.08-1.40 (m, 10 H), 1.45-1.62 (m, 4 H), 1.80-1.90 (m, 2 H), 2.08-2.14 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.8 (t), 14.0 (q), 19.1 (t), 22.1 (t), 27.2 (t), 28.4 (t), 36.4 (t), 182.4 (s); exact mass *m/z* calcd for $C_{10}H_{20}O_2{}^{120}Sn$ (M - C_2H_4) 292.0485, found 292.0488.

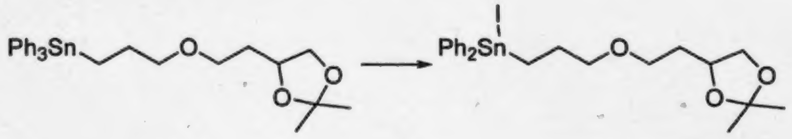
[3-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethoxy]propyl]-triphenylstannane (17.3).



17.2 **17.3**

Aqueous NaOH (50%, 10 mL) was added to a solution of 3-(triphenylstannyl)propan-1-ol (**17.2**) (3.48 g, 8.5 mmol) and 4-(2-bromoethyl)-2,2-dimethyl-1,3-dioxolane (**17.1**) (2.00 g, 9.6 mmol) in THF (20 mL). The reaction mixture was heated at reflux (70 °C) for 48 h and cooled to room temperature. The mixture was diluted with water (50 mL) and then extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1:19 EtOAc-hexane, gave compound **17.3** (1.35 g, 47%) as a colorless oil: FTIR (CD_2Cl_2 cast) 3063, 2985, 1480 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.15 (s, 3 H), 1.17 (s, 3 H), 1.50-1.75 (m, 4 H), 1.92-2.01 (m, 2 H), 3.30-3.47 (m, 5 H), 3.91-4.08 (m, 2 H), 7.15-7.60 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 9.1 (t), 27.5 (q), 28.5 (t), 28.6 (q), 32.7 (t), 69.4 (t), 71.4 (t), 75.4 (t), 75.7 (d), 110.2 (s), 130.3 (d), 130.7 (d), 138.9 (d), 141.2 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{34}NaO_3{}^{120}Sn$ (M + Na) 561.1428, found 561.1432.

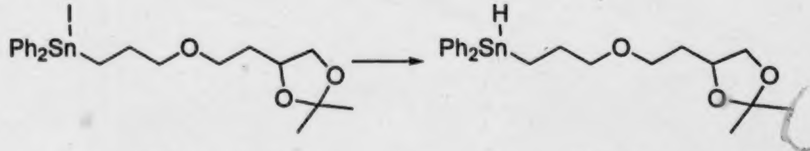
[3-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethoxy]propyl]-iododiphenylstannane (17.4).



17.3 **17.4**

A solution of I_2 (0.57 g, 2.3 mmol) in PhH (20 mL) was added dropwise over ca. 30 min to a stirred solution of stannane **17.3** (1.22 g, 2.3 mmol) in PhH (10 mL). Stirring was continued for 1 h at room temperature and the solvent was concentrated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:4 EtOAc-hexane, gave iodide **17.4** (1.27 g, 94%) as a colorless oil: ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.20 (s, 3 H), 1.22 (s, 3 H), 1.30-1.40 (m, 2 H), 1.95-2.03 (m, 2 H), 2.11-2.20 (m, 2 H), 3.08-3.20 (m, 3 H), 3.50-3.70 (m, 4 H), 7.38-7.50 (m, 6 H), 7.60-7.80 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 17.5 (t), 25.7 (q), 26.9 (q), 27.1 (t), 32.9 (t), 68.7 (t), 69.3 (t), 71.9 (t), 73.1 (d), 108.9 (s), 129.0 (d), 129.9 (d), 136.4 (d), 141.2 (s); exact mass *m/z* calcd for $C_{22}H_{29}O_3{}^{120}Sn$ (M - I) 461.1139, found 461.1146.

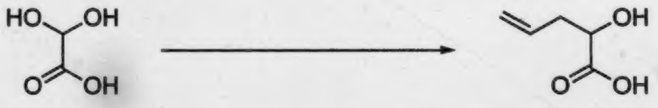
[3-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethoxy]propyl]-diphenylstannane (17.5).



17.4 **17.5**

A solution of iodostannane **17.4** (150 mg, 0.26 mmol) in Et_2O (5 mL) was added slowly to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (10 mg, 0.26 mmol) in Et_2O (10 mL) over ca. 5 min. The ice bath was left in place but not recharged and stirring was continued for 3 h. The reaction mixture was cooled to 0 °C and slowly quenched by addition of aqueous NaOH (1.0 N, 1 mL). The mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford stannane **17.5** (112 mg, 95%) as a colorless oil: ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.28 (s, 3 H), 1.37 (s, 3 H), 1.38-1.45 (m, 2 H), 1.60-1.80 (m, 2 H), 1.92-2.00 (m, 2 H), 3.38-3.45 (m, 5 H), 3.95-4.00 (m, 1 H), 4.02-4.10 (m, 1 H), 6.18-6.20 (m, 1 H), 7.35-7.40 (m, 6 H), 7.44-7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 5.9 (t), 25.6 (q), 26.9 (q), 30.8 (t), 32.9 (t), 68.7 (t), 69.3 (t), 71.9 (t), 73.1 (d), 108.9 (s), 129.0 (d), 129.9 (d), 136.4 (d), 141.2 (s).

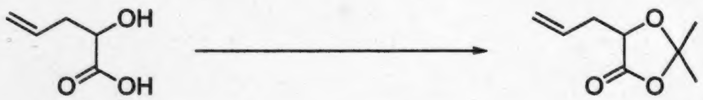
2-Hydroxy-4-pentenoic Acid (19.2).[35]



19.1 **19.2**

Glyoxylic acid hydrate (1.90 g, 20.0 mmol) and allyl bromide (2.50 mL, 28.0 mmol) were added to a stirred suspension of $BiCl_3$ (8.80 g, 28.0 mmol) and Zn (2.77 g, 42.0 mmol) in THF (60 mL) at 0 °C. The ice bath was removed and stirring was continued for 16 h. The mixture was quenched by addition of aqueous hydrochloric acid (1.0 M, 40 mL) and then extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue was over silica gel (2.5 x 25 cm), using 7:3 EtOAc-hexane, gave acid **19.2** (2.38 g, 95%) as white crystals: ^1H NMR ($CDCl_3$, 500 MHz) δ 2.44-2.52 (m, 1 H), 2.59-2.66 (m, 1 H), 4.35 (dd, J = 4.6, 6.6 Hz, 1 H), 5.15-5.21 (m, 2 H), 5.75-5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 38.4 (t), 69.8 (d), 119.4 (t), 131.8 (d), 178.6 (s).

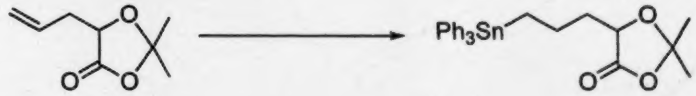
2,2-Dimethyl-5-(2-propenyl)-1,3-dioxolan-4-one (19.3).



19.2 **19.3**

Acid **19.2** (6.00 g, 51.7 mmol) was dissolved in 2,2-dimethoxypropane (150 mL). Pyridinium *p*-toluenesulfonate (0.50 g, 1.99 mmol) was added, and the mixture was stirred for 5 h (TLC control). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:19 EtOAc-hexane, gave acetonide **19.3** (6.14 g, 76%) as a colorless oil: FTIR ($CDCl_3$ cast) 2918, 1797 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 3 H), 1.60 (s, 3 H), 2.45-2.54 (m, 1 H), 2.62-2.70 (m, 1 H), 4.45 (dd, J = 4.6, 6.6 Hz, 1 H), 5.16-5.26 (m, 2 H), 5.77-5.88 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.9 (q), 27.2 (q), 35.8 (t), 73.8 (d), 110.7 (s), 119.2 (d), 131.9 (t), 172.6 (s); exact mass *m/z* calcd for $C_8H_{12}O_3$ 156.0786, found 156.0783.

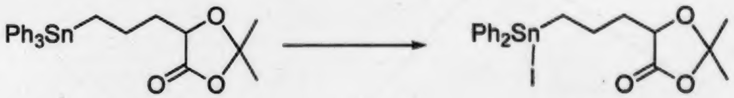
2,2-Dimethyl-5-[3-(triphenylstannyl)propyl]-1,3-dioxolan-4-one (19.4).



19.3 **19.4**

A solution of **19.3** (1.56 g, 10.0 mmol) in dry PhH (10 mL) was added to freshly prepared Ph_3SnH (5.26 g, 15.0 mmol). AIBN (10 mg) was added to the mixture, which was then heated at 85 °C for 10 h (TLC control; N_2 atmosphere). Evaporation of the solvent, and rapid (no more than 30 min) flash chromatography of the residue over silica gel (3 x 25 cm), using 1:49 EtOAc-hexane, gave stannane **19.4** (3.29 g, 65%) as a colorless oil: FTIR ($CDCl_3$ cast) 3063, 1792, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (two s, each 3 H), 1.50-1.53 (m, 2 H), 1.75-1.97 (m, 4 H), 4.35 (dd, J = 4.0, 7.0 Hz, 1 H), 7.33-7.39 (m, 9 H), 7.46-7.59 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.4 (t), 22.3 (t), 25.8 (q), 27.1 (q), 35.9 (t), 73.6 (d), 110.4 (s), 128.5 (d), 130.0 (d), 137.0 (d), 138.6 (s), 173.2 (s); exact mass m/z calcd for $C_{26}H_{28}O_3{}^{120}Sn$ 508.1060, found 508.1056.

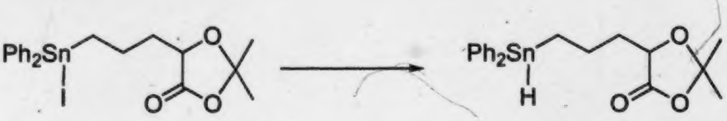
2,2-Dimethyl-5-[3-[iodo(diphenyl)stannyl]propyl]-1,3-dioxolan-4-one (19.5).



19.4 **19.5**

A solution of I_2 (0.64 g. 2.5 mmol) in PhH (30 mL) was added over 30 min to a stirred solution of **19.4** (1.28 g, 2.5 mmol) in PhH (20 mL). Stirring was continued for 5-10 h (TLC control), and the solvent was concentrated. Rapid (less than 30 min) flash chromatography of the residue over silica gel (2 x 15 cm), using 1:4 EtOAc-hexane, gave **19.5** (1.31 g, 93%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3065, 1790, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 3 H), 1.53 (s, 3 H), 1.72-2.04 (m, 6 H), 4.34-4.39 (m, 1 H), 7.35-7.70 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.2 (t), 22.7 (t), 25.8 (q), 27.2 (q), 35.0 (t), 73.6 (d), 110.6 (s), 129.0 (d), 130.1 (d), 136.1 (d), 137.0 (s), 173.0 (s); exact mass *m/z* calcd for $C_{20}H_{23}IO_3{}^{120}Sn$ 557.9714, found 557.9729.

2,2-Dimethyl-5-[3-(diphenylstannyl)propyl]-1,3-dioxolan-4-one (19.6).

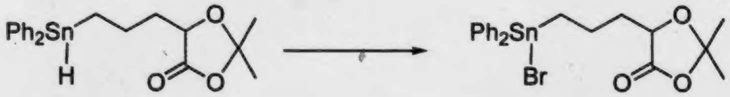


19.5 **19.6**

NaBH$_4$ (44 mg, 1.1 mmol) was added to a stirred and cooled (0 °C) solution of **19.5** (636 mg, 1.1 mmol) in dry MeOH (20 mL). Stirring was continued for 3 h at 0 °C, and the reaction mixture was then quenched by addition of EtOAc (20 mL) and water (20 mL). The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with brine, dried (MgSO$_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 1:4 EtOAc-hexane, gave stannane **19.6** (484 mg, 98%) as a colorless oil: FTIR (CD_2Cl_2 cast) 3068, 1792, 1429 cm^{-1};

^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.35-1.41 (m, 2 H), 1.49 (s, 3 H), 1.52 (s, 3 H), 1.75-1.97 (m, 4 H), 4.34-4.38 (m, 1 H), 6.16 (t, *J* = 1.8 Hz, 1 H), 7.31-7.37 (m, 6 H), 7.45-7.56 (m, 4 H); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 16.9 (t), 21.5 (t), 25.8 (q), 27.2 (q), 35.2 (t), 73.6 (d), 110.6 (s), 129.0 (d), 130.2 (d), 135.7 (d), 138.4 (s), 172.9 (s); exact mass (electrospray) *m/z* calcd for $C_{20}H_{24}NaO_3{}^{120}Sn$ (M + Na) 455.0645, found 455.0654.

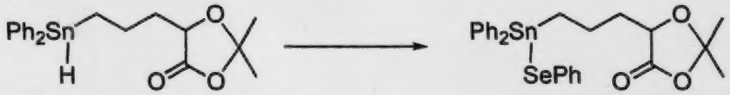
2,2-Dimethyl-5-[3-[bromo(diphenyl)stannyl]propyl]-1,3-dioxolan-4-one (20.1).



19.6 **20.1**

1-Bromopropane (0.5 mL) was added to a solution of stannane **19.6** (217 mg, 0.5 mmol) and AIBN (3 mg, 0.02 mmol) in PhMe (8 mL). The mixture was then heated at 115 °C for 3 h, cooled to room temperature, and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 EtOAc-hexane, gave bromide **20.1** (153 mg, 60%) as a colorless oil: FTIR (CHCl$_3$ cast) 3066, 1789, 1430 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.49 (s, 3 H), 1.54 (s, 3 H), 1.66-2.04 (m, 6 H), 4.34-4.39 (m, 1 H), 7.38-7.68 (m, 10 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 16.7 (t), 21.8 (t), 25.7 (q), 27.1 (q), 35.0 (t), 73.5 (d), 110.6 (s), 129.0 (d), 130.2 (d), 135.8 (d), 137.9 (s), 173.0 (s); exact mass *m/z* calcd for $C_{20}H_{23}{}^{81}BrO_3{}^{120}Sn$ 511.9832, found 511.9825.

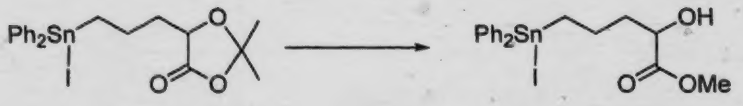
2,2-Dimethyl-5-[3-[diphenyl(phenylseleno)stannyl]-propyl]-1,3-dioxolan-4-one (20.2).



19.6 **20.2**

Stannane **19.6** (227 mg, 0.5 mmol) and AIBN (5 mg, 0.03 mmol) in PhMe (5 mL, plus 3 mL as a rinse) were added in one portion to a refluxing solution of (3aα,6α,6aα)-hexahydro-6-(phenylseleno)-2*H*-cyclopenta[b]furan-2-one[37] (see entry 7, Table 1) (106 mg, 0.4 mmol) in PhMe (3 mL). Refluxing was continued for 10 h, and the solvent was then concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:9 EtOAc-hexane, gave **20.2** (152 mg, 69%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3064, 2925, 1791, 1576, 1474 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40-1.45 (m, 2 H), 1.48 (s, 3 H), 1.50 (s, 3 H), 1.65-1.88 (m, 4 H), 4.28 (dd, *J* = 4.0, 7.0 Hz, 1 H), 7.02 (t, *J* = 7.5 Hz, 2 H), 7.12 (t, *J* = 7.4 Hz, 1 H), 7.30-7.50 (m, 12 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.9 (t), 22.2 (t), 25.9 (q), 27.2 (q), 35.5 (t), 73.5 (d), 110.4 (s), 124.6 (s), 126.6 (d), 128.6 (d), 128.7 (d), 129.4 (d), 136.4 (d), 136.5 (d), 138.2 (s), 172.9 (s); exact mass (electrospray) *m/z* calcd for $C_{26}H_{28}NaO_3{}^{80}Se^{120}Sn$ (M + Na) 611.0123, found 611.0118.

Methyl 5-[Iodo(diphenyl)stannyl]-2-hydroxypentanoate (20.5).



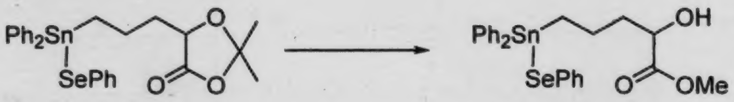
19.5 **20.5**

(a) Aqueous LiOH (1.0 M, 2 mL) was added to a stirred solution of compound **19.5** (133 mg, 0.24 mmol). Stirring was continued for 1 h, and the mixture was acidified with concentrated hydrochloric acid. The precipitate was collected, washed with CH_2Cl_2, and dried under oil pump vacuum. This solid (62 mg) was then suspended in a mixture of MeOH (2 mL) and PhMe (5 mL), and Me_3SiCHN_2 (2.0 M in hexane, 0.3 mL, 0.60 mmol) was added dropwise with stirring. Stirring was continued for 15 min. AcOH (0.5 mL) was added to destroy the excess of Me_3SiCHN_2, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 10 cm), using EtOAc, gave **20.5** (20 mg, 16%). See following experiment for characterization data.

(b) $TsOH \cdot H_2O$ (3 mg) was added to a stirred solution of compound **19.5** (40 mg, 0.07 mmol) in MeOH (3 mL). Stirring was continued for 1.5 h and the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave **20.5** (19.6 mg, 50%) as a colorless oil: FTIR ($CDCl_3$ cast) 3425 (br), 3064, 1733, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65-2.00 (m, 6 H), 2.72 (br s, 1 H), 3.72 (s, 3 H), 4.15 (d, J = 7.1 Hz, 1 H), 7.33-7.43 (m, 6

H), 7.54-7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.2 (t), 22.5 (t), 37.4 (t), 52.6 (q), 70.0 (d), 128.9 (d), 130.0 (d), 136.1 (d), 137.5 (s), 175.3 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{21}INaO_3{}^{120}Sn$ (M + Na) 554.9450, found 554.9454.

Methyl 5-[(Diphenyl)(phenylseleno)stannyl]-2-hydroxypentanoate (20.6).



20.2 **20.6**

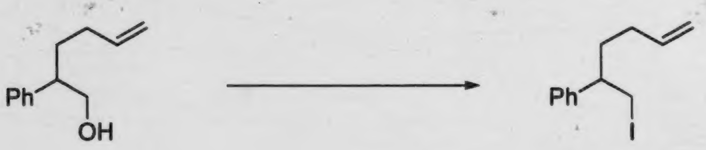
Conversion of **20.2** into **20.6** was done in two slightly different ways:

(a) After the LiOH hydrolysis of a crude mixture from reduction of 1-(phenylseleno)dodecane (59 mg, 0.11 mmol) (entry 6, Table 1), the aqueous LiOH layer was acidified with concentrated hydrochloric acid, and the precipitate was collected, washed with CH_2Cl_2, and dried under oil pump vacuum. The solid (63 mg) was then suspended in a mixture of MeOH (2 mL) and PhMe (5 mL), and Me_3SiCHN_2 (2.0 M in hexane, 0.25 mL, 0.50 mmol) was added dropwise with stirring. Stirring was continued for 15 min. AcOH (0.5 mL) was added to destroy the excess of Me_3SiCHN_2, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:9 EtOAc-hexane, gave **20.6** (20 mg, 31%) as a yellow oil: FTIR ($CHCl_3$ cast) 3485, 3063, 1958, 1735, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37-1.85

(m, 6 H), 2.57 (d, *J* = 5.7 Hz, 1 H), 3.71 (s, 3 H), 4.07-4.13 (m, 1 H), 7.02 (t, *J* = 7.4 Hz, 2 H), 7.12 (tt, *J* = 1.2, 7.4 Hz, 1 H), 7.30-7.54 (m, 12 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (t), 22.0 (t), 38.2 (t), 52.5 (q), 69.9 (d), 124.7 (s), 126.5 (d), 128.6 (d), 128.6 (d), 129.3 (d), 136.4 (d), 136.5 (d), 138.4 (s), 175.4 (s); exact mass *m/z* calcd for $C_{18}H_{21}O_3{}^{120}Sn$ (M - PhSe) 405.0513, found 405.0523.

(b) Anhydrous K_2CO_3 (3 mg, 0.02 mmol) was added to a stirred solution of **20.2** (94 mg, 0.16 mmol) in MeOH (5 mL), and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:19 EtOAc-hexane, gave **20.6** (65 mg, 72%) as a yellow oil.

[1-(Iodomethyl)-4-pentenyl]benzene (21.5).

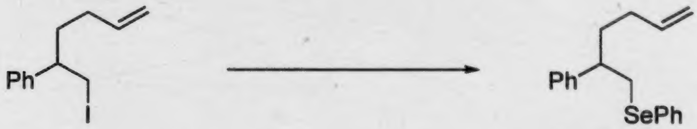


21.5

Ph_3P (1.44 g, 5.5 mmol) and imidazole (0.375 g, 5.5 mmol) were added in one portion to a stirred solution of 2-phenyl-5-hexen-1-ol[38] (0.485 g, 2.8 mmol) in CH_2Cl_2 (20 mL).[39] Stirring was continued for 10 min, and I_2 (1.40 g, 5.5 mmol) was added to the mixture. Stirring was continued for 3 h, and the reaction mixture was then diluted with saturated aqueous $Na_2S_2O_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 15 cm),

using 1:99 EtOAc-hexane, gave **21.5** (751 mg, 95%) as a colorless oil: FTIR ($CDCl_3$ cast) 3062, 2929, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.67-1.76 (m, 1 H), 1.85-2.03 (m, 3 H), 2.82-2.89 (m, 1 H), 3.32-3.41 (m, 2 H), 4.92-4.97 (m, 2 H), 5.69-5.78 (m, 1 H), 7.13-7.16 (m, 2 H), 7.22-7.34 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.7 (t), 31.6 (t), 34.9 (t), 47.6 (d), 115.0 (t), 127.0 (d), 127.4 (d), 128.5 (d), 137.8 (d), 142.7 (s); exact mass *m/z* calcd for $C_{12}H_{15}I$ 286.0219, found 286.0215.

[(2-Phenylhex-5-enyl)seleno]benzene (21.6).

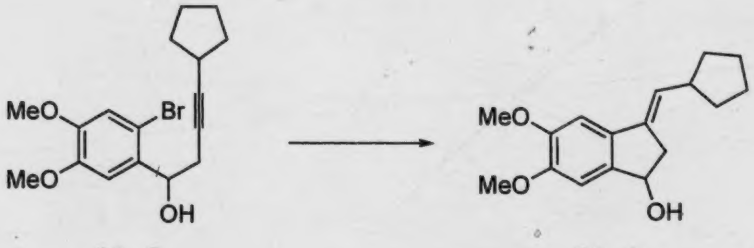


21.5 **21.6**

$NaBH_4$ (52 mg, 1.35 mmol) was added to a stirred solution of **21.5** (250 mg, 0.87 mmol) and PhSeSePh (136 mg, 0.44 mmol) in MeOH (7 mL), more MeOH (3 mL) being used as a rinse to transfer all the $NaBH_4$. Stirring was continued for 10 h and the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using hexane, gave **21.6** (230 mg, 83%) as a colorless oil: FTIR ($CDCl_3$ cast) 3072, 3027, 2926, 1640, 1579, 1477 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.68-1.76 (m, 1 H), 1.82-2.00 (m, 3 H), 2.82-2.88 (m, 1 H), 3.12-3.19 (m, 2 H), 4.87-4.94 (m, 2 H), 5.67-5.76 (m, 1 H), 7.10-7.44 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 31.5 (t), 35.2 (t), 35.3 (t), 45.6 (d), 114.7 (t), 126.62 (d), 126.64 (d), 127.5 (d), 128.4 (d), 128.9 (d), 130.8 (s), 132.5 (d), 138.1 (d), 143.9 (s); exact mass *m/z* calcd for $C_{18}H_{20}{}^{80}Se$ 316.0730, found

316.0727.

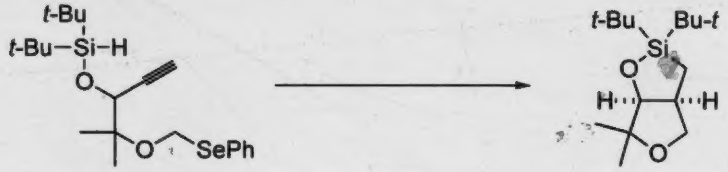
3-Cyclopentylmethylene-2,3-dihydro-5,6-dimethoxy-1*H*-inden-1-ol (21.9).



21.8 **21.9**

The general thermal procedure for radical cyclization was followed, using **21.8**[40] (83.5 mg, 0.23 mmol) in PhH (10 mL), stannane **19.6** (143 mg, 0.33 mmol) and AIBN (2 mg, 0.01 mmol) in PhH (8 mL, plus 2 mL as a rinse), an addition time of 5 h, and an arbitrary reflux time of 5 h after the addition. The general basic workup procedure was followed, using aqueous LiOH (1.0 M, 2 mL) in THF (2 mL), and a reaction time of 3 h. Flash chromatography of the crude product over silica gel (1 x 15 cm), using 3:7 EtOAc-hexane, gave **21.9** (58.8 mg, 90%) as a colorless oil (a single isomer, stereochemistry not established): FTIR (CH_2Cl_2 cast) 3383, 2949, 1605, 1500 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.25-2.00 (m, 9 H), 2.46-2.56 (m, 1 H), 2.58-2.73 (m, 1 H), 2.96-3.08 (m, 1 H), 3.41 (two s, each 3 H), 5.05 (dd, J = 3.2, 7.3 Hz, 1 H), 5.82 (dt, J = 2.3, 9.1 Hz, 1 H), 6.80 (s, 1 H), 6.91 (s, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 25.5 (t), 33.7 (t), 40.2 (t), 40.8 (d), 55.3 (q), 73.4 (d), 102.8 (d), 107.9 (d), 123.1 (d), 133.7 (s), 137.9 (s), 139.5 (s), 150.9 (s), 151.1 (s); exact mass m/z calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1571.

cis-2,2-Bis(1,1-dimethylethyl)hexahydro-6,6-dimethylfuro[3,4-*d*]-1,2-oxasilole (21.11).

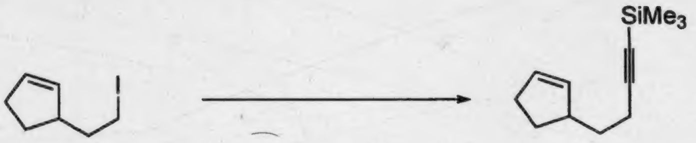


21.10 **21.11**

The general thermal procedure for radical cyclization was followed, using **21.10**[41] (42.5 mg, 0.10 mmol) in PhH (3 mL), stannane **19.6** (65 mg, 0.15 mmol) and AIBN (2 mg, 0.01 mmol) in PhH (6 mL, plus 1 mL as a rinse), an addition time of 7 h, and an arbitrary reflux time of 5 h after the addition. The general basic workup procedure was followed, using aqueous LiOH (1.0 M, 1 mL) in THF (2 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (1 x 10 cm), using 1:19 EtOAc-hexane, gave **21.11** (20.9 mg, 78%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2931, 2857, 1472, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.62 (dd, J = 2.8, 15.5 Hz, 1 H), 1.00 (s, 9 H), 1.06 (s, 9 H), 1.06-1.10 (m, 1 H), 1.14 (s, 3 H), 1.28 (s, 3 H), 2.90-3.00 (m, 1 H), 3.46 (dd, J = 6.6, 9.0 Hz, 1 H), 4.00 (t, J = 8.9 Hz, 1 H), 4.08 (d, J = 6.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.1 (s), 19.7 (s), 21.2 (t), 22.4 (q), 25.6 (q), 27.5 (q), 27.9 (t), 41.9 (d), 73.1 (t), 84.2 (s), 89.1 (d); exact mass m/z calcd for $C_{15}H_{30}O_2Si$ 270.2015, found 270.2017.

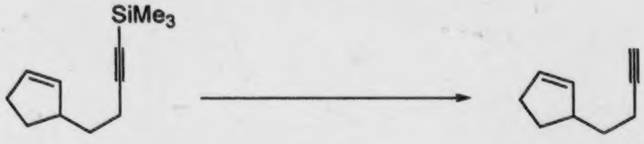
4-(2-Cyclopenten-1-yl)-1-butyne (21.12).

(a) [4-(2-Cyclopenten-1-yl)but-1-ynyl]trimethylsilane.



n-BuLi (2.5 M in hexane, 7.10 mL, 17.7 mmol) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of ethynyltrimethylsilane (2.45 mL, 17.0 mmol) in THF (100 mL). Stirring at -78 °C was continued for 1.5 h, and neat 3-(2-iodoethyl)cyclopentene[42] (4.00 g, 18.1 mmol) was added dropwise over ca. 30 min (syringe pump). The cold bath was removed and stirring was continued for 10 h. The reaction mixture was quenched by addition of water (100 mL), and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of residue over silica gel (2.5 x 20 cm), using hexane, gave recovered starting material (2.67 g) and [4-(2-cyclopenten-1-yl)but-1-ynyl]trimethyl-silane (1.02 g, 88% corrected for recovered starting material) as a colorless oil: FTIR (CH_2Cl_2 cast) 3051, 2956, 2175, 1614, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.12 (s, 9 H), 1.35-1.42 (m, 1 H), 1.45-1.53 (m, 1 H), 1.58-1.66 (m, 1 H), 1.99-2.07 (m, 1 H), 2.20-2.36 (m, 4 H), 2.69-2.77 (m, 1 H), 5.63-5.73 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 0.3 (q), 18.4 (t), 29.5 (t), 32.0 (t), 34.9 (t), 44.9 (d), 84.3 (s), 107.6 (s), 130.7 (d), 134.3 (d); exact mass *m/z* calcd for $C_{12}H_{20}Si$ 192.1334, found 192.1337.

(b) 4-(2-Cyclopenten-1-yl)-1-butyne (21.12).



21.12

Aqueous NaOH (2.0 N, 20 mL) was added in one portion to a stirred solution of [4-(2-cyclopenten-1-yl)but-1-ynyl]trimethylsilane (1.00 g, 5.2 mmol) in MeOH (30 mL). Stirring was continued for 3 h, and the mixture was then extracted with pentane (3 x 50 mL). The combined organic extracts were washed with water and brine, and then dried ($MgSO_4$). Evaporation of the solvent at 1 atmosphere (short Vigreux column) and flash chromatography of the residue over silica gel (1 x 15 cm), using pentane, gave **21.12**[43] (0.30 g, 49%) as a colorless oil: ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.8 (t), 29.4 (t), 31.9 (t), 34.6 (t), 44.6 (d), 68.0 (d), 84.7 (s), 130.9 (d), 134.2 (d).

IV References and Notes

1 Clive, D. L. J. *Encyclopedia of Reagents for Organic Synthesis* Paquette, L. A. Ed.; Wiley: New York, **1994**, Vol. 8, 5412-5416.

2 *Chem. & Eng. News*. **1997**, Oct. 27, p 23.

3 Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743-745.

4 Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859-1866.

5 Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*, Academic Press: London, **1992**.

6 Jacobus, J.; Leibner, J. E. *J. Org. Chem.* **1979**, *44*, 449-450.

7 Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471-472.

8 Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140-3157.

9 Davis, D. D.; Johnson, H. T. *J. Organomet. Chem.* **1975**, *86*, 75-87.

10 Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200-7201.

11 Kuivilla, H. G.; Menapace, W. *J. Org. Chem.* **1963**, *28*, 2165-2167.

12 Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554-2555.

13 Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303-304.

14 Review on the use of polymethylhydrosiloxane as stoichiometric reductant: Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381-3391.

15 E. g., see: (a) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4-5. (b) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751-6752.

16 (a) Gerlach, M.; Jördens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, *56*, 5971-5972. (b) Gerigk, U.; Gerlach, M.; Neumann, W. P.; Vieler, R.; Weintritt, V. *Synthesis* **1990**, 448-452.

17 Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957-2968.

18 Rai, R.; Collum, D. B. *Tetrahedron Lett.* **1994**, *35*, 6221-6224.

19 Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem.* **1993**, *58*, 3046-3050.

20 Clive, D. L. J.; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607-2609.

21 (a) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531-2532. (b) Hadida, S.; Super, M. S.; Beckman, E. J.; Curran, D. P. *J. Am. Chem. Soc.* **1997**, *119*, 7406-7407. (c) Horner, J. H.; Martinez, F. N.; Newcomb, M.; Hadida, S.; Curran, D. P. *Tetrahedron Lett.* **1997**, *38*, 2783-2786. (d) Ryu, I.; Niguma, T.; Minakata, S.; Komatsu, M.; Hadida, S.; Curran, D. P. *Tetrahedron Lett.* **1997**, *38*, 7883-7886. (e) Curran, D. P.; Hadida, S.; Kim, S. Y.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 6607-6615.

22 Review on alternatives to stannanes: Baguley, P. A.; Walton, J. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072-3082.

23 Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188-194.

24 Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1993**, *58*, 6838-6842.

25 Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 225-235.

26 Mikami, S; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1853-1855.

27 Zard, S. Z. *Angew. Chem. Int. Ed.* **1997**, *36*, 672-685.

28 Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1.* **1975**, 1574-1585.

29 Solladie, G; Kovenski, J; Colobert, F. *Tetrahedron Asym.* **1993**, *4*, 2173-2178.

30 Kuivila, H. G.; Beumel, O. F. Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1246-1250.

31 Conil, M. F.; Jousseaume, B.; Noiret, N.; Pereyre, M. *Organometallics* **1994**, *13*, 24-25.

32 Sugai, S.; Ikawa, H.; Hasegawa, Y.; Yoshida, S.; Kutsuma, T.; Akaboshi, S. *Chem. Pharm. Bull.* **1984**, *32*, 967-976.

33 Van der Kerk, G. J. M.; Noltes, J. G.; Luijten, J. G. A. *J. Appl. Chem.* **1957**, *7*, 366-369.

34 Cf. Wardell, J. L.; Wigzell, J. McM. *J. Chem. Soc., Dalton Trans.* **1982**, 2321-2326.

35 Wada, M.; Honna, M.; Kuramoto, Y.; Miyoshi, N. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2265-2267.

36 Supplied by Chemical Dynamics Corporation (South Plainfield, NJ).

37 Clive, D. L. J.; Russell, C. G.; Chittattu, G.; Singh, A. *Tetrahedron* **1980**, *36*, 1399-1408.

38 Jung, M. E.; Vu, B. T. *J. Org. Chem.* **1996**, *61*, 4427-4433.

39 Cf. Berkenbusch, T.; Brückner, R. *Tetrahedron* **1998**, *54*, 11461-11470.

40 Compound **21.8** was a gift from Haikang Yang of this laboratory.

41 Clive, D. L. J.; Yang, W.; MacDonald, A.; Wang, Z.; Cantin, M. *J. Org. Chem.* **2001**, *66*, 1966-1983.

42 This compound is reported, without experimental details, in Curran, D. P.; Yu. H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343-7366. We prepared the iodide from the corresponding alcohol (Lee, C. C.; Wong, E. W. C. *Tetrahedron* **1965**, *21*, 539-545) by treatment with PPh_3, I_2 and imidazole.

43 Piers, E.; Chong, M. J.; Howard, M. *Tetrahedron* **1989**, *45*, 363-380.

Chapter Two

Total Synthesis of (±)-1-*epi*-Hamigeran B, (±)-Hamigeran B and (-)-Hamigeran B

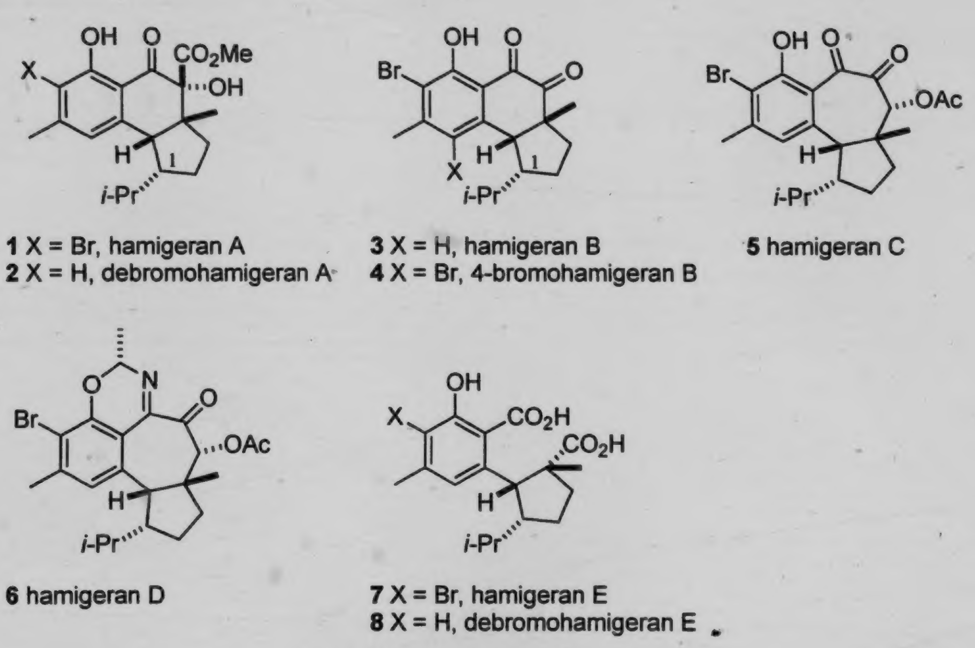
I, Introduction

1.1 General

Research on bioactive natural compounds isolated from marine organisms has been studied extensively for over 30 years,[1] and a number of potentially important pharmaceutical leads have been uncovered. Moreover, marine organisms have provided a seemingly endless parade of novel structures which challenge synthetic chemists to develop new methods to synthesize these structures and to provide sufficient material for further biological studies. One such set of intriguing compounds is the subject of this section of the thesis.

In 1999, Cambie and coworkers isolated[2] a group of new compounds from the poecilosclerid marine sponge *Hamigera tarangaensis* Bergquist and Fromont (family Anchinoidae, syn. Phorbasidae) collected in shallow waters near the Hen and Chicken Islands off the north western coast of New Zealand.

These eight phenolic compounds (**1** – **8**, Scheme 1) have a unique carbon skeleton in which a substituted aromatic nucleus is fused to a [4.3.0] or a [5.3.0] bicyclic system featuring a *cis* junction and bearing three or more stereogenic centers. The structures, which are shown in Scheme 1, were assigned mainly from extensive NMR examination.[2] The absolute configuration of hamigeran A (**1**) was determined by single crystal X-ray analysis[3] and the authors assumed that all other hamigerans have the same absolute configuration.



1 X = Br, hamigeran A
2 X = H, debromohamigeran A
3 X = H, hamigeran B
4 X = Br, 4-bromohamigeran B
5 hamigeran C
6 hamigeran D
7 X = Br, hamigeran E
8 X = H, debromohamigeran E

Scheme 1

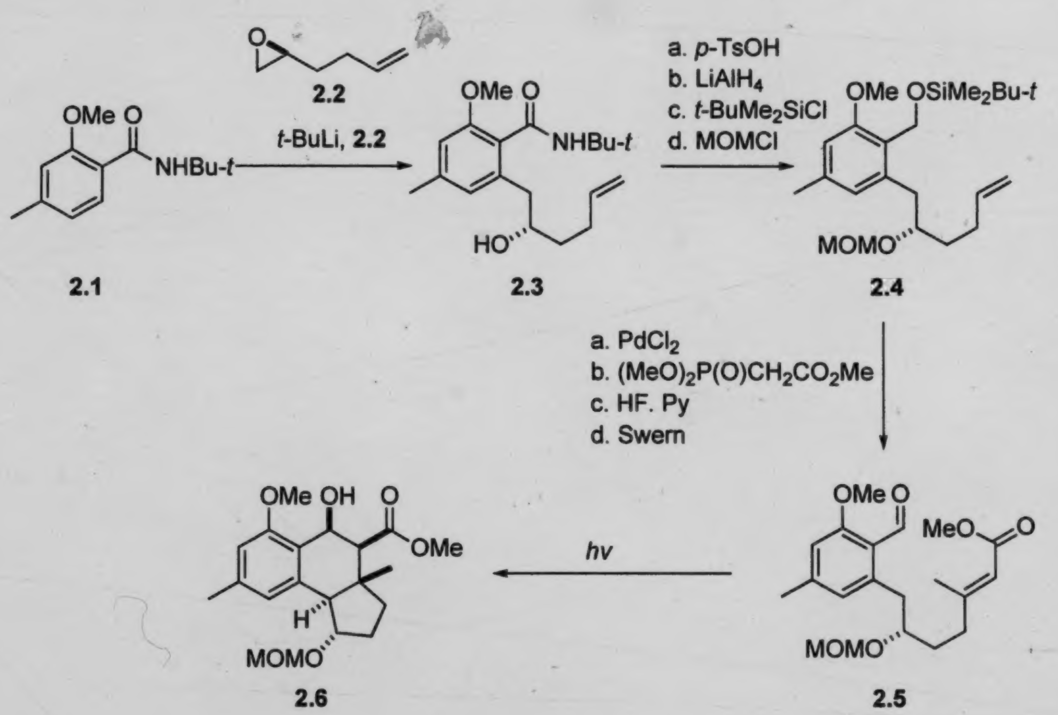
Evaluation of these compounds for biological activity[2] showed that hamigeran A (**1**), hamigeran B (**3**), 4-bromohamigeran B (**4**), hamigeran C (**5**) and hamigeran D (**6**) have *in vitro* antitumor activity against P-388 leukemia cell lines with IC_{50} values between 8 μM and 31.6 μM. Compounds **3**, **4**, **5**, and **6** inhibited the growth of the Gram-positive bacterium *Bacillus subtilis*. Compounds **3**, **5**, and **6** also showed slight activity against *Trichophyton mentagrophytes*. The most pronounced biologically activity was observed for compound **3**, as it had 100% virus inhibition against both the Herpes and Polio viruses, with only slight cytotoxicity. Although hamigeran B is one of the structurally simpler members of the group, it is the most biological active one. Consequently, it has drawn the most intense attention as a synthetic target. When we began our own work no synthesis had been described, but before we had finished our synthesis, the Nicolaou research group[4,5] reported the first synthesis of (-)-hamigeran B and several other members of this family in 2001. The full details of their synthesis were also described in a recent full article.[6] After we published our synthesis of (±)-hamigeran B,[7] a route to (-)-1-*epi*-hamigeran B was reported by the Mehta group[8] in the middle of 2003. And a few months ago, a third total synthesis of (-)-hamigeran B was published by the Trost group.[9] These studies are summarized in the following sections, where the atom numbering of hamigeran B is used for all compounds so that the isopropyl group is always at the position labeled C(1).

1.2 Nicolaou's Synthesis of (-)-Hamigeran B.

Based on their methodology of photoenolization of substituted benzaldehydes and *in situ* Diels-Alder trapping of the resulting hydroxy-*o*-quinodimethanes, the Nicolaou group was able to finish the total synthesis of (-)-hamigeran B, as well as several of its congeners.[4,5]

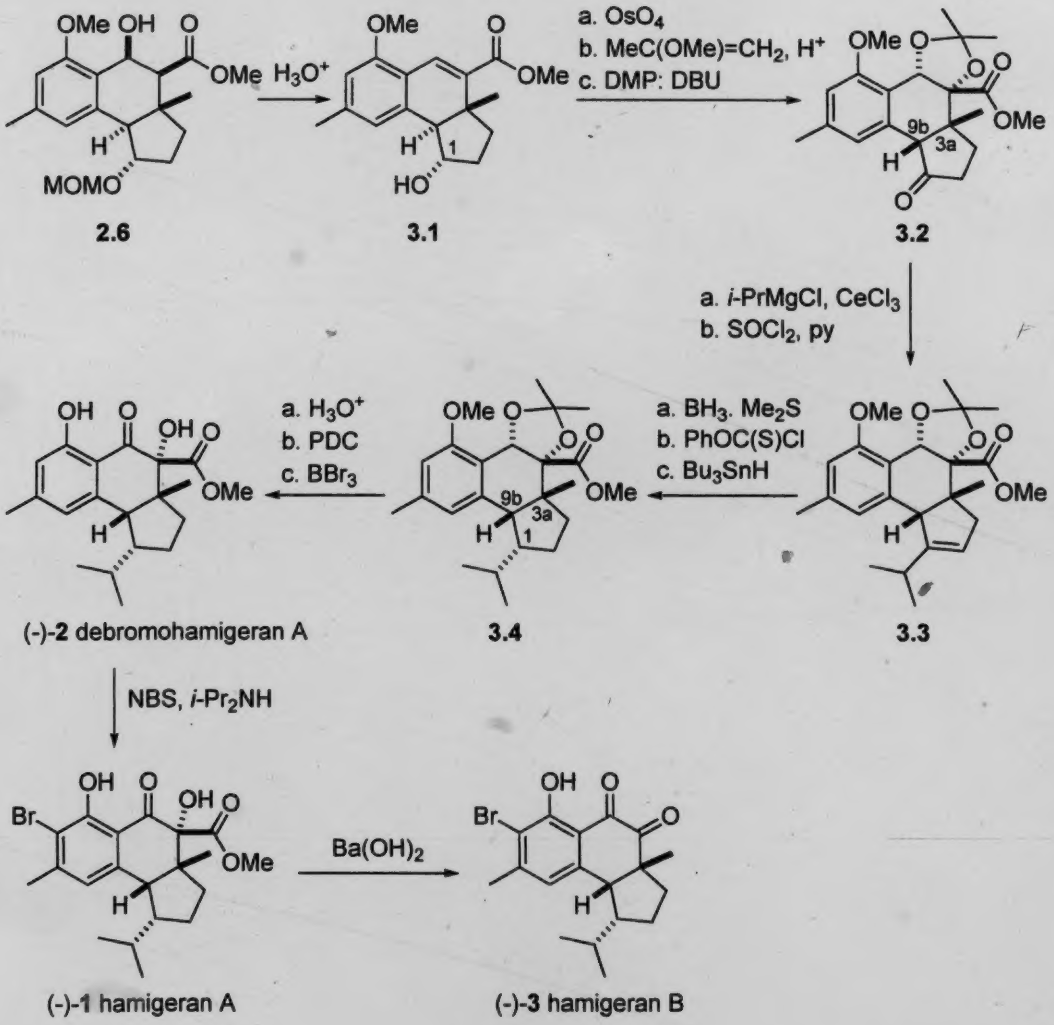
Their synthesis started with the known benzamide **2.1** (Scheme 2). The dianion, which was obtained by treatment of benzamide **2.1** with 2 equiv of *t*-BuLi, opened the enantiomerically enriched epoxide (*S*)-**2.2** to give the secondary alcohol **2.3**. Acid-induced intramolecular attack of this alcohol at the amide group, followed by reduction with $LiAlH_4$ and selective stepwise protection of the resulting diol, afforded **2.4**. Wacker oxidation of **2.4**, followed by Horner-Emmons-Wadsworth reaction of the resulting methyl ketone with $(MeO)_2P(O)CH_2CO_2Me$, desilylation and Swern oxidation, furnished benzaldehyde **2.5** as an *E*/*Z* mixture. The key step (**2.5** → **2.6**) is the photochemically induced intramolecular Diels-Alder reaction to form the benzannulated system of the hamigerans. Scheme

2 shows the photochemical result for the *E*-olefin only, but the product from the *Z*-isomer was also used, as the next step converts both products to the same compound.



Scheme 2

At this point, treatment of the key building block **2.6** (Scheme 3) with methanolic HCl at 60 °C led both to dehydration and cleavage of the MOM protecting group (**2.6 → 3.1**). Olefin **3.1** was dihydroxylated stereoselectively from the under face, and the resulting vicinal diol was protected as its acetonide. The free hydroxyl group at C(1) was then oxidized with the Dess-Martin reagent, and a base induced isomerization at C(9b) now afforded ketone **3.2** with *cis* ring fusion at C(3a) and C(9b). Reaction of this ketone with *i*-PrMgCl in the presence of $CeCl_3$ introduced the required isopropyl group at C(1), and then treatment with $SOCl_2$ and pyridine gave olefin **3.3** as the major product.



Scheme 3

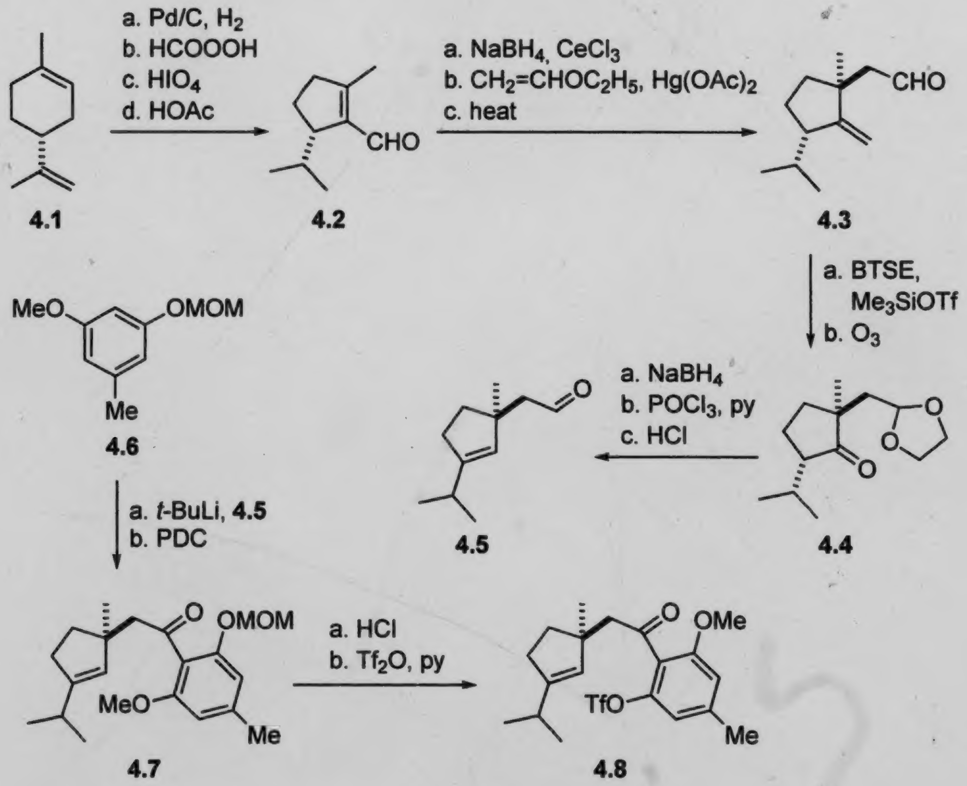
The crucial stereochemistry at C(1) was set by hydroboration of olefin **3.3** under sonication conditions. After oxidative workup, the desired 1*R*,2*R* alcohol can be separated as the major product (11:6 ratio against the *endo* addition product). The free hydroxyl group at C(2) was then removed under standard Barton deoxygenation conditions to give acetonide **3.4** with the correct stereochemistry at C(1), C(3a) and C(9b).

The acetonide protecting group of **3.4** was removed; and PDC oxidation of the benzylic position followed by BBr_3-induced demethylation of the phenolic methyl ether led to the first natural product, (-)-debromohamigeran A [(-)-**2**]. (-)-Hamigeran A [(-)-**1**] was obtained by NBS-mediated selective bromination at the *ortho* position of **2**. Finally, treatment of (-)-hamigeran A (**1**) with $Ba(OH)_2$ in $MeOH/H_2O$ brought about a cascade of reactions, including saponification, decarboxylation and oxidation at C(4) to furnish (-)-hamigeran B [(-)-**3**].

1.3 Mehta's Synthesis of 1-*epi*-(-)-Hamigeran B.

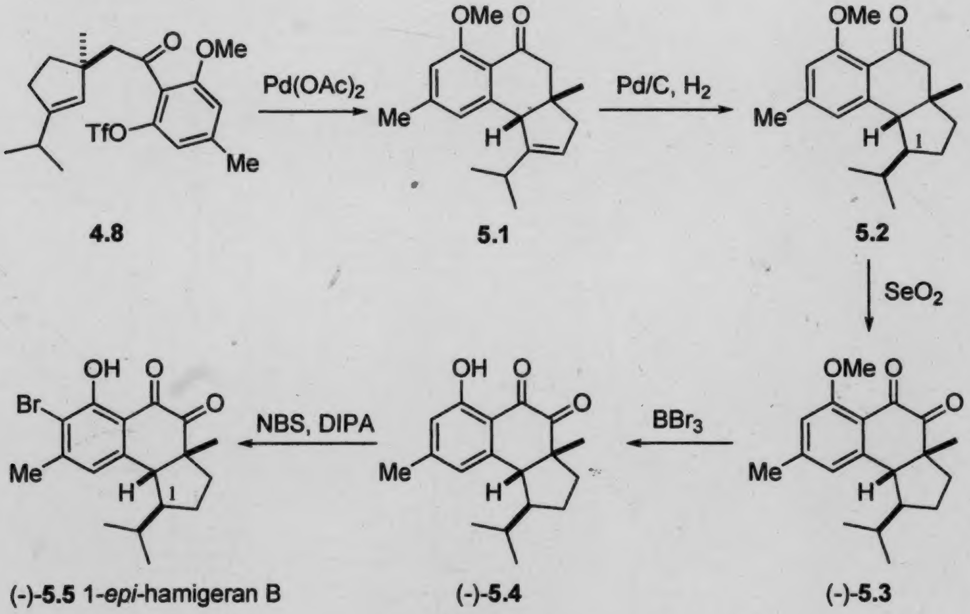
After we finished our synthesis of (±)-hamigeran B,[7] Mehta and Shinde reported their approach to optically pure (-)-1-*epi*-hamigeran B in the middle of 2003.[8]

Their synthesis (Scheme 4) began with abundantly available (+)-limonene **4.1**. Hydrogenation, followed by oxidation with performic acid, gave a mixture of *trans*-*p*-menth-1,2-diols. Cleavage of the diols with periodic acid and cyclization of the resultant keto aldehyde with acetic acid afforded aldehyde **4.2**.[10] This aldehyde was reduced and the resulting alcohol transformed into a vinyl ether by Hg^{2+} catalyzed transetherification. Thermolysis of the vinyl ether afforded aldehyde **4.3** via Claisen rearrangement.[11] Protection of the aldehyde group by reaction with 1,2-bis(trimethylsilyloxy)ethane in the presence of catalytic Me_3SiOTf, followed by ozonolysis of the terminal olefin gave ketone **4.4**. Reduction of the carbonyl group and further dehydration of the resulting alcohol, followed by removal of the aldehyde protecting group, delivered the unsaturated aldehyde **4.5**. Directed metalation of the aromatic compound **4.6** and reaction with **4.5**, followed by PDC oxidation, furnished **4.7**. The MOM group was then transformed in two steps into the optically pure key triflate **4.8**.



Scheme 4

At this stage an intramolecular Heck coupling led to tricyclic compound **5.1** (Scheme 5). Surprisingly, catalytic hydrogenation of this compound occurred exclusively from the more hindered *endo* face of the molecule with Pd-C, to furnish compound **5.2** with the C(1) isopropyl group being epimeric with respect to hamigeran B (**3**). Changes to the catalyst and solvent did not alter the stereochemical outcome. With compound **5.2** in hand, selenium dioxide oxidation delivered optically pure diketone (-)-**5.3**. The methyl ether moiety was deprotected to give phenol (-)-**5.4** and finally, selective bromination with NBS in the presence of a catalytic amount of *i*-Pr_2NH afforded (-)-1-*epi*-hamigeran B [(-)-**5.5**].



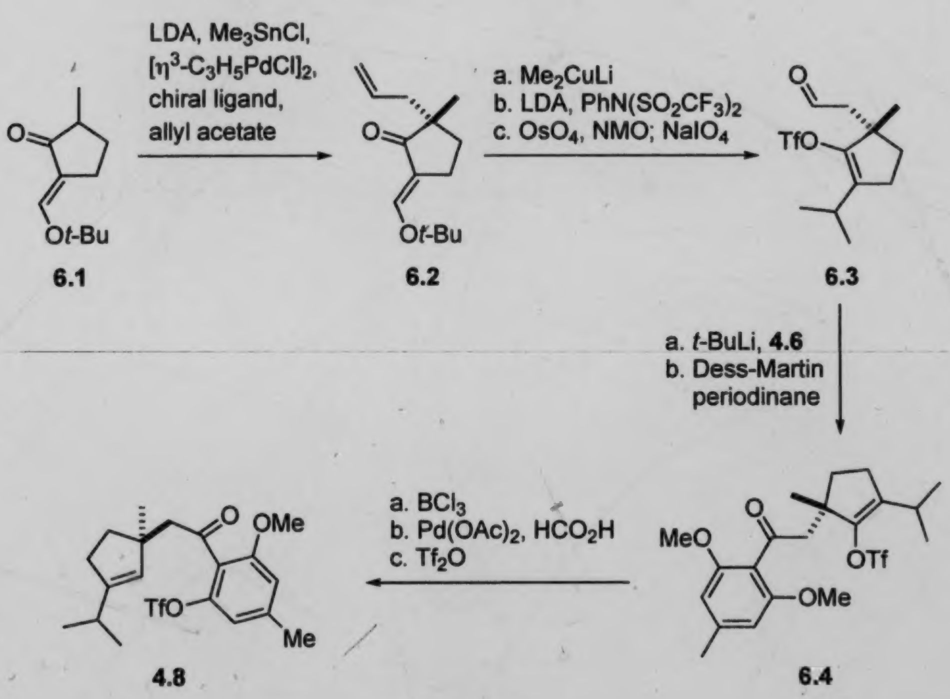
Scheme 5

1.4 Trost's Synthesis of (-)-Hamigeran B.

Very recently, the Trost group reported their approach to optically pure (-)-hamigeran B.[9]

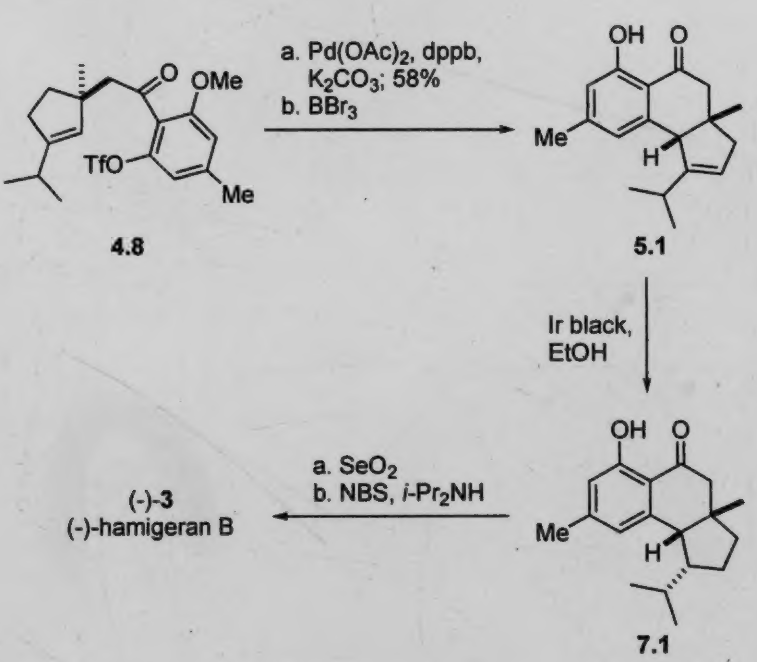
The key steps of their synthesis – construction of the tricyclic system and the stereochemical centers of hamigeran B – are very similar to Mehta's route, although they have used a different approach to make the substrate for the Heck reaction (Scheme 6). The lithium enolate formed from **6.1**, itself derived in a one-pot reaction of 2-methylcyclopentanone and ethyl formate first with *t*-BuONa and then with sulfuric acid, was subjected to asymmetric alkylation using the Trost methodology[12] to afford ketone

6.2 with >90% ee. The alkoxymethylene group of **6.2** was then converted into an isopropyl group upon treatment with lithium dimethylcuprate. The reaction was quenched by addition of a triflating agent, leading to direct formation of a vinyl triflate. At this point, oxidative cleavage of the pendant double bond gave aldehyde **6.3**. Direct reaction of this aldehyde with lithiated **4.6**, followed by oxidation with the Dess-Martin periodinane, gave ketone **6.4**. One of the aryl ethers was demethylated and the vinyl triflate was reductively cleaved [$Pd(OAc)_2$, HCO_2H]. The free phenol was then converted into the required triflate **4.8**.



Scheme 6

The required intramolecular Heck reaction was effected by using dppb as the ligand, and K_2CO_3 as base. The expected alkene **5.1** was obtained in 58% yield (Scheme 7). The phenolic hydroxyl was liberated by demethylation, and hydrogenation of the resulting alkene over Pd-C, gave the exact same product (**5.2**, Scheme 5) as Mehta *et al.* obtained in their synthesis of 1-*epi*-hamigeran B.



Scheme 7

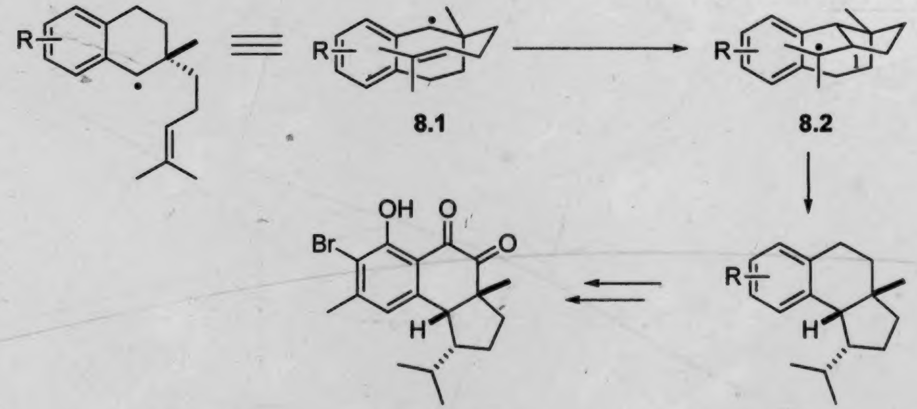
The Trost group assumed that the undesired *epi* product was formed by an equilibration in the semihydrogenation intermediate, a process that was made possible because the final reductive elimination step is slow. Therefore, they used iridium as the catalyst since it was known to minimize such equilibrations.[13] As expected, hydrogenation with this catalyst now gave ketone **7.1** with the correct stereochemistry at all stereogenic centers. Oxidation of **7.1** with selenium dioxide and then selective bromination at the *ortho* position to the phenol completed the total synthesis.

It is noteworthy that the Trost group, because of its extensive experience with organometallic chemistry, was able to overcome the serious obstacle posed by the stereochemistry of the isopropyl group, while the Mehta team was not able to solve the problem.

II Results and Discussion

2.1 Synthesis of (±)-1-*epi*-Hamigeran B.

The most obvious synthetic difficulty presented by hamigeran B is the stereochemistry at C(1), because the bulky isopropyl substituent extends into the more hindered face of the structure. This orientation probably disqualifies methods that rely on stereochemical equilibration at C(1).



8.1

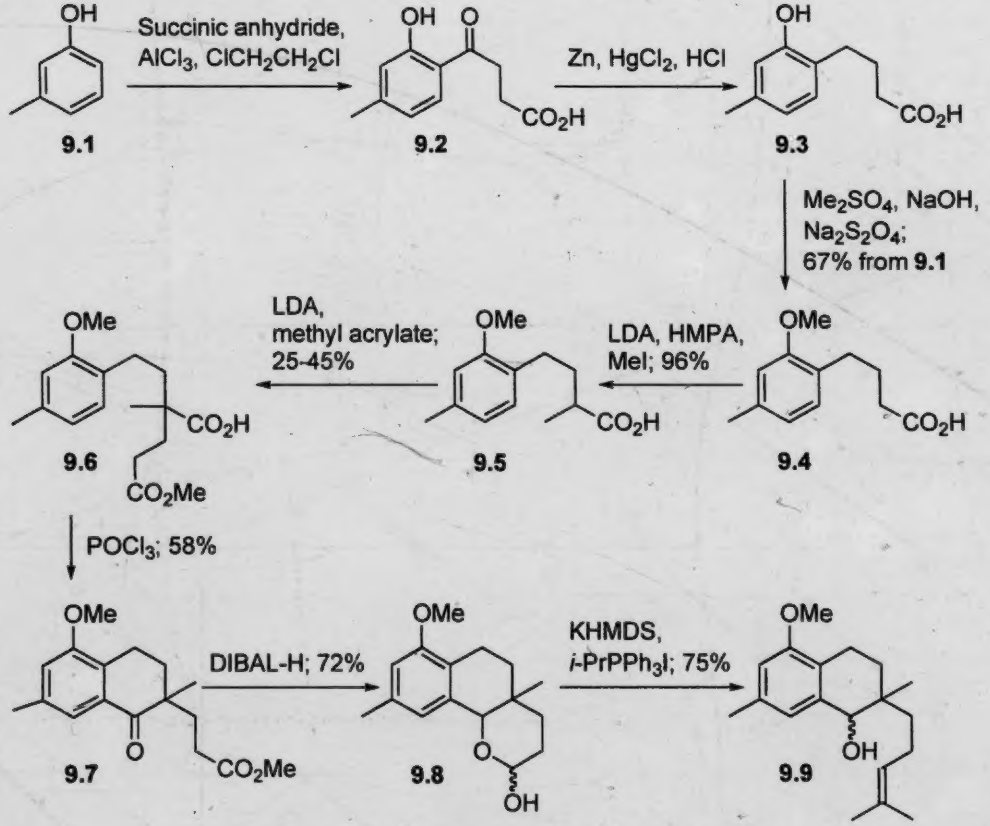
8.2

3 hamigeran B

8.3

Scheme 8

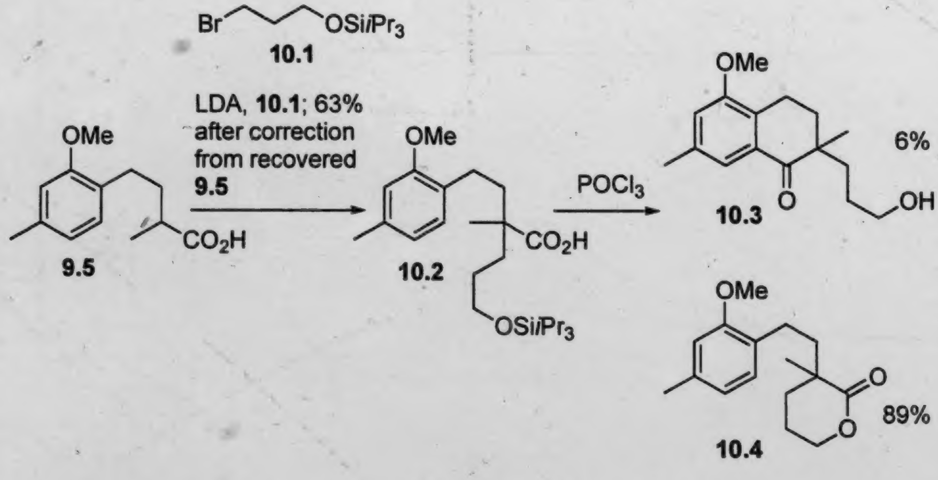
Our first approach to hamigeran B was based on the idea of using radical cyclization. As summarized in Scheme 8, we expected that the benzylic radical **8.1** would cyclize via a 5-*exo-trigonal* pathway, with the isopropyl group occupying an equatorial conformation (**8.1** → **8.2**). Such a ring closure would lead to the tricyclic compound **8.3** with the required stereochemistry at C(1), and this compound could then serve as a key intermediate and be transformed eventually into hamigeran B (**3**).



Scheme 9

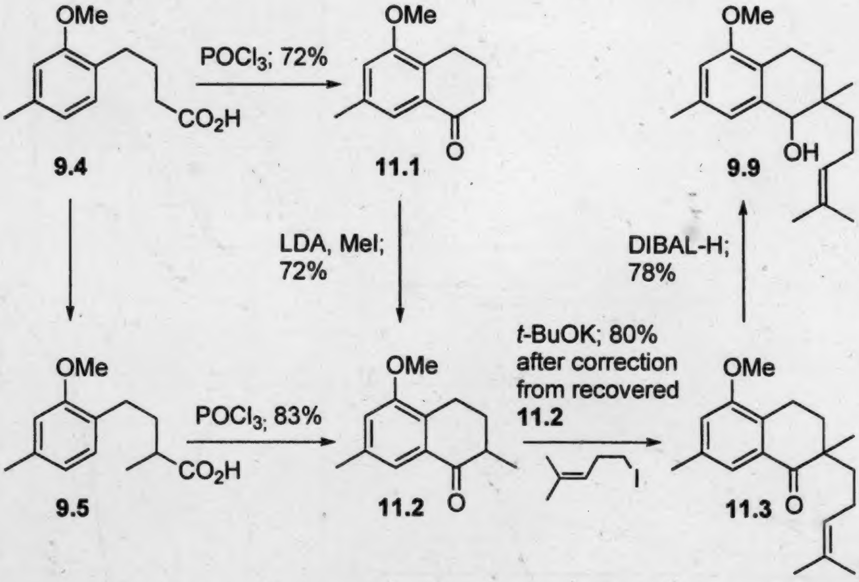
To generate an appropriate radical precursor, we started our synthesis with *m*-cresol (**9.1**). As shown in Scheme 9, the *m*-cresol was first converted into keto acid **9.2** by Friedel-Crafts acylation with succinic anhydride.[14] Clemmensen reduction[15] of **9.2** gave the phenolic acid **9.3**, and *O*-methylation, using Me_2SO_4 in aqueous NaOH in the presence of a catalytic amount of $Na_2S_2O_4$,[14] then afforded acid **9.4** in 67% overall yield from **9.1**. Compound **9.4** was easily methylated[16] by treatment with LDA and MeI in the presence of HMPA to give acid **9.5** in 96% yield. A second alkylation α to the carboxyl group (LDA, methyl acrylate, 25-45%) afforded the dialkylated compound **9.6** with the required side chains. This compound was made to cyclize by treatment with $POCl_3$ in $ClCH_2CH_2Cl$ at reflux, to produce the tetralone **9.7** in 58% yield. DIBAL-H reduction of **9.7** gave us the expected lactols **9.8**. These lactols were inseparable, and were treated with $Ph_3P^+CH(CH_3)_2I^-$ and excess KHMDS to furnish benzylic alcohols **9.9** in 75% yield.[17]

Some reactions shown in Scheme 9 gave low yields, especially for the conversion of compound **9.5** into **9.6**; therefore, we made some modifications to this route. Our first attempt in this regard was the alkylation of acid **9.5**. The acid was treated with 2 equiv of LDA and the bromo compound **10.1** was then added to the resulting dianion as electrophile, to give dialkylated acid **10.2** in 63% yield (Scheme 10). However, when compound **10.2** was subjected to cyclization with $POCl_3$, only a 6% yield of the desired tetralone (**10.3**) was obtained, but lactone **10.4** was isolated in 89% yield.



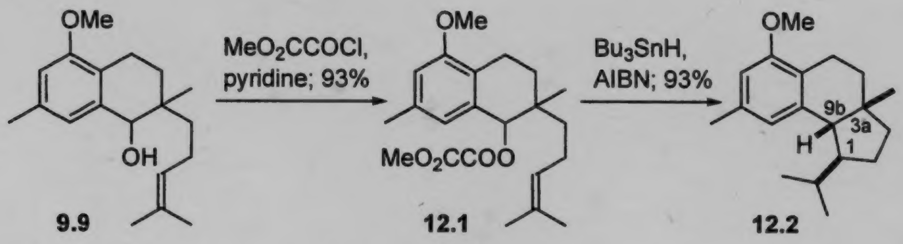
Scheme 10

In another series of experiments, we treated acid **9.4** with POCl$_3$ in Cl$_2$CHCHCl$_2$, and obtained tetralone **11.1** in 72% yield (Scheme 11). Methylation α to this ketone under standard conditions (LDA, -78 °C, MeI, 72%) gave compound **11.2**. Alternatively, tetralone **11.2** was also made from acid **9.5** by treatment with POCl$_3$ (83% yield). Obviously, the route **9.4** → **9.5** → **11.2** provided a higher overall yield over these 2 steps.



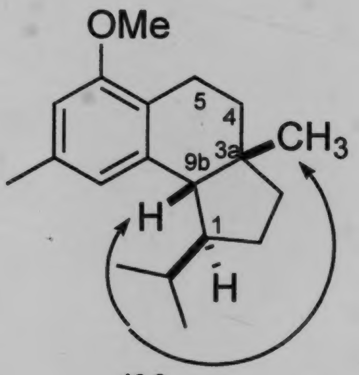
Scheme 11

The required second side chain was then installed by treating **11.2** with t-BuOK[18] and 2-methyl-5-iodo-2-pentene[19] in PhMe at reflux. It is worth mentioning here that we also tried this reaction with other bases, such as LDA and LHMDS. Unfortunately, they gave none of the desired product at all. The dialkylated tetralone **11.3** was reduced with DIBAL-H to afford alcohol **9.9** in 78% yield as a single isomer. The stereochemistry of this alcohol was not determined, but we assume that the hydride was delivered from the face of the (smaller) methyl group.



Scheme 12

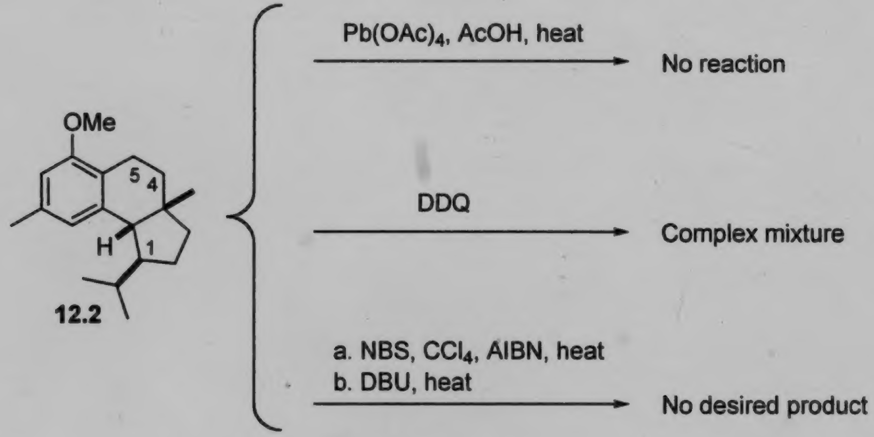
At this point the stage has been set to generate a radical at the benzylic position of alcohol **9.9**, our hope being that this radical would cyclize to provide the desired stereochemistry. Accordingly, alcohol **9.9** was converted into radical precursor **12.1**[20] by treatment of MeO$_2$CCOCl in the presence of pyridine (Scheme 12). Slow addition of a benzene solution of Bu$_3$SnH and AIBN to a refluxing solution of compound **12.1** in the same solvent, produced in high yield what was eventually characterized as the tricyclic compound **12.2**.



12.2

Scheme 13

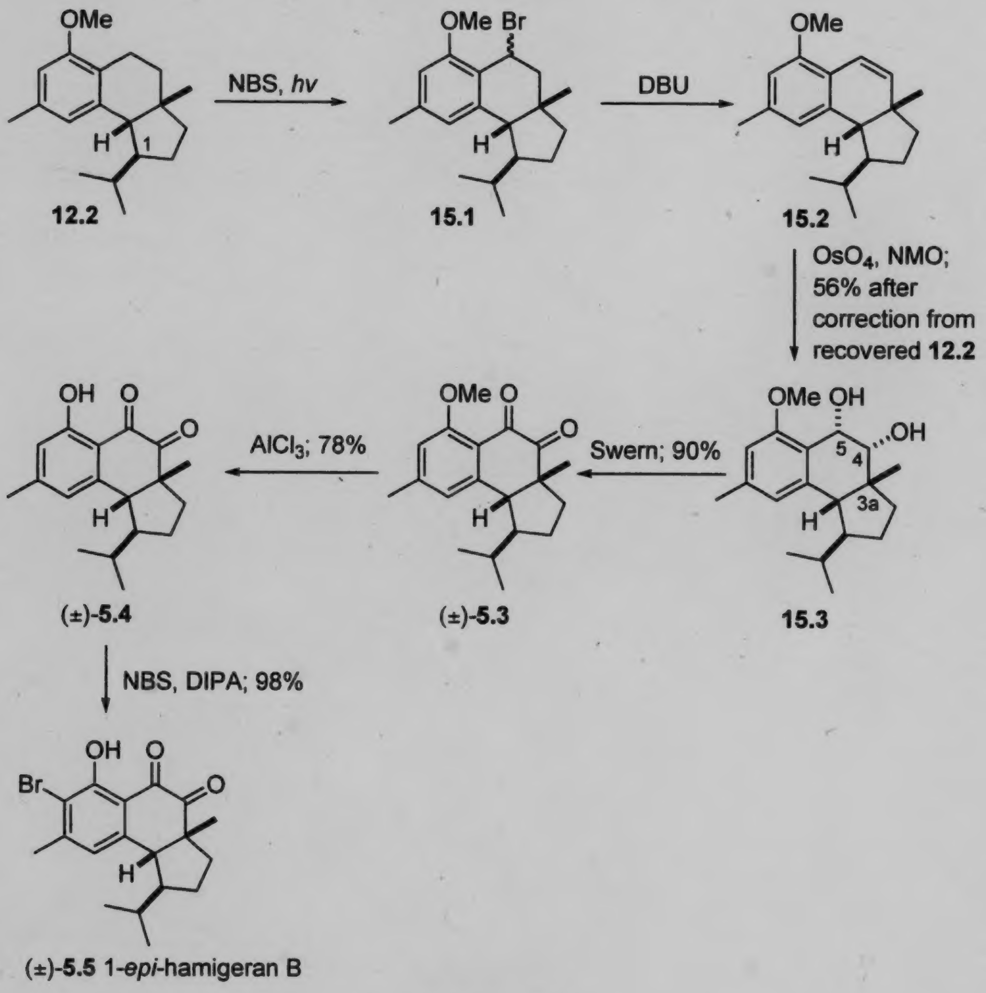
To examine if the stereochemical outcome of the radical cyclization followed our expectation, we performed extensive NMR studies on **12.2**. From T-ROESY measurements we could establish that the proton at C(9b) and the C(3a) angular methyl substituent are *cis* to each other based on the fact that strong T-ROESY cross-peaks can be observed between these two substituents (Scheme 13). Unfortunately, we were unable to determine the relative stereochemistry at C(1) by these studies because of the complexity of the spectrum; however, we proved that compound **12.2** has the undesired stereochemistry at C(1) at a later stage by single crystal X-ray analysis of a derivative [Scheme 15, compound (±)-**5.3**].



Scheme 14

Although we did not know the stereochemistry at C(1) at this stage, we decided to continue with the sequence and to generate the carbonyl functionalities at C(4) and C(5) first. However, attempts to generate a C(4)-C(5) double bond were unsuccessful when we heated **12.2** with $Pb(OAc)_4$[21] in AcOH or with DDQ (Scheme 14). Heating **12.2** with 1 equiv of NBS and a catalytic amount of AIBN in CCl_4, followed by heating with DBU,[22] also gave no trace of the desired product.

Finally, benzylic bromination of **12.2** was achieved by irradiation in the presence of NBS[23] (Scheme 15), but the presumed products (**15.1**) were too unstable to allow purification; accordingly, the crude material was treated directly with DBU, so as to form alkene **15.2**, which was obtained mixed with unchanged **12.2**.



Scheme 15

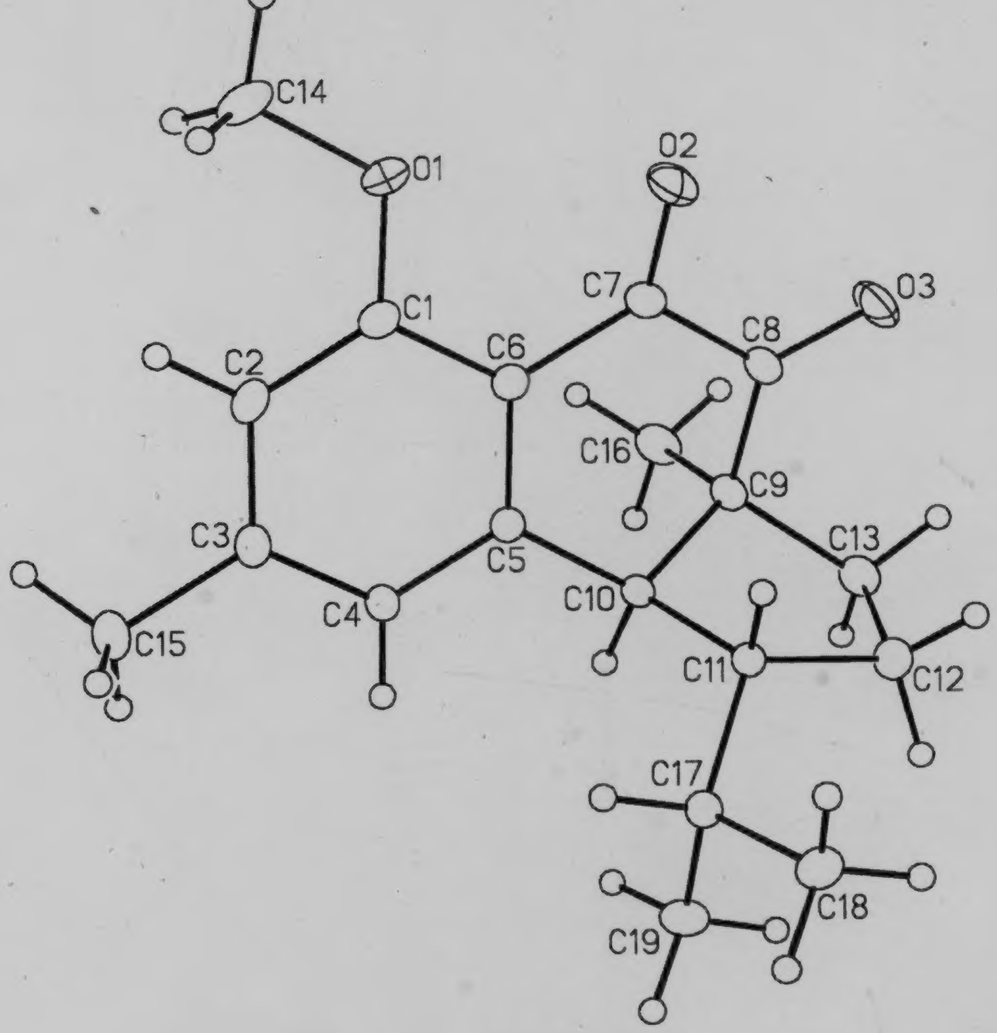


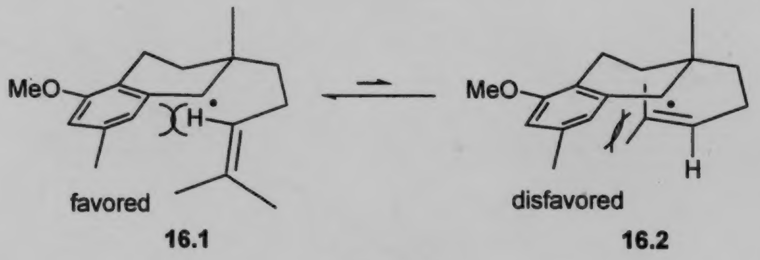
Figure 1 Crystal structure of (±)-**5.3**

The crude mixture was subjected to dihydroxylation, under standard conditions (catalytic OsO_4, stoichiometric NMO),[24] and at this stage, pure diol **15.3** could be isolated from the unreacted **12.2** (56% overall yield, after correction for recovered **12.2**). The stereochemical assignment to the hydroxyls in **15.3** was made on the basis of NOE measurements (cross-peaks between the proton at C(5) and the C(3a) methyl substituent). Swern oxidation of this diol led to the crystalline diketone (±)-**5.3**, whose structure was assigned by single crystal X-ray analysis (Figure 1).

Surprisingly, treatment of (±)-**5.3** with BBr_3 failed to give the corresponding demethylation product (±)-**5.4**. However, this step could be done by treating diketone (±)-**5.3** with $AlCl_3$ in CH_2Cl_2 at reflux (77%).[25] Finally, bromination at 0 °C with NBS in the presence of catalytic *i*-Pr_2NH, conditions known[26] to favor *ortho* bromination, gave us racemic 1-*epi*-hamigeran B [(±)-**5.5**] in high yield.

The unexpected outcome of this approach – which led to the 1-*epi* series – prompted us to modify our synthetic plan, and those studies are summarized in the following section.

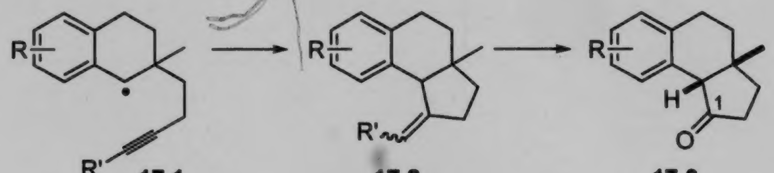
2.2 Synthesis of (±)-Hamigeran B.



Scheme 16

Our previous studies showed that with the isopropyl substituent installed, the 5-*exo-trigonal* radical cyclization did not give us the desired stereochemistry at C(1). This undesired result is probably due to the fact that steric interaction between the large isopropyl moiety and the tetralone ring system (Scheme 16) makes transition state **16.1**, in which the large substituent is *exo*, more favored than the *endo* conformation **16.2**. Consequently, the more thermodynamically favored product **12.2** is produced (Scheme 12).

To avoid this steric interaction, a slight modification was examined, as shown in Scheme 17. We planned to do the radical cyclization onto a triple bond (**17.1** → **17.2**), and the resulting tricyclic product would then be subjected to ozonolysis (**17.2** → **17.3**). The resulting ketone **17.3** might provide opportunities for introducing the isopropyl group with the correct stereochemistry by a sequence involving Grignard addition, dehydration and hydrogenation. Although this part of our plans are similar to the reported method of the Nicolaou group, it should be remembered that at this stage no synthesis had been described in the literature, and, in the event, this route was not used.

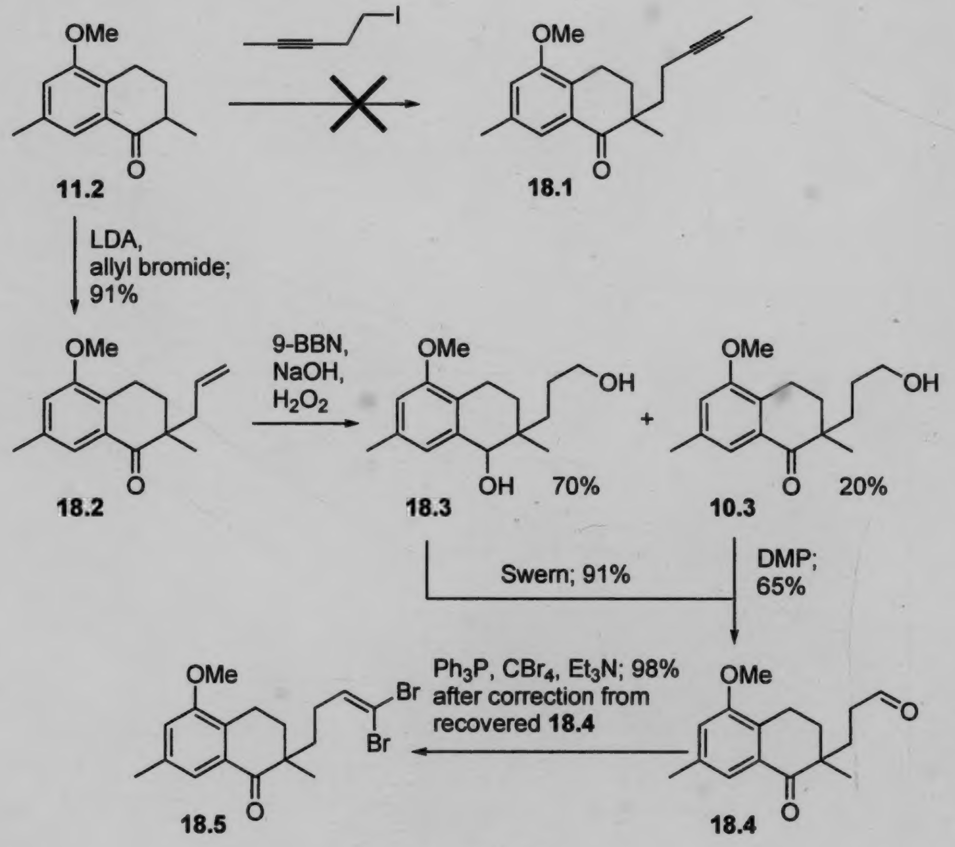


17.1 **17.2** **17.3**

Scheme 17

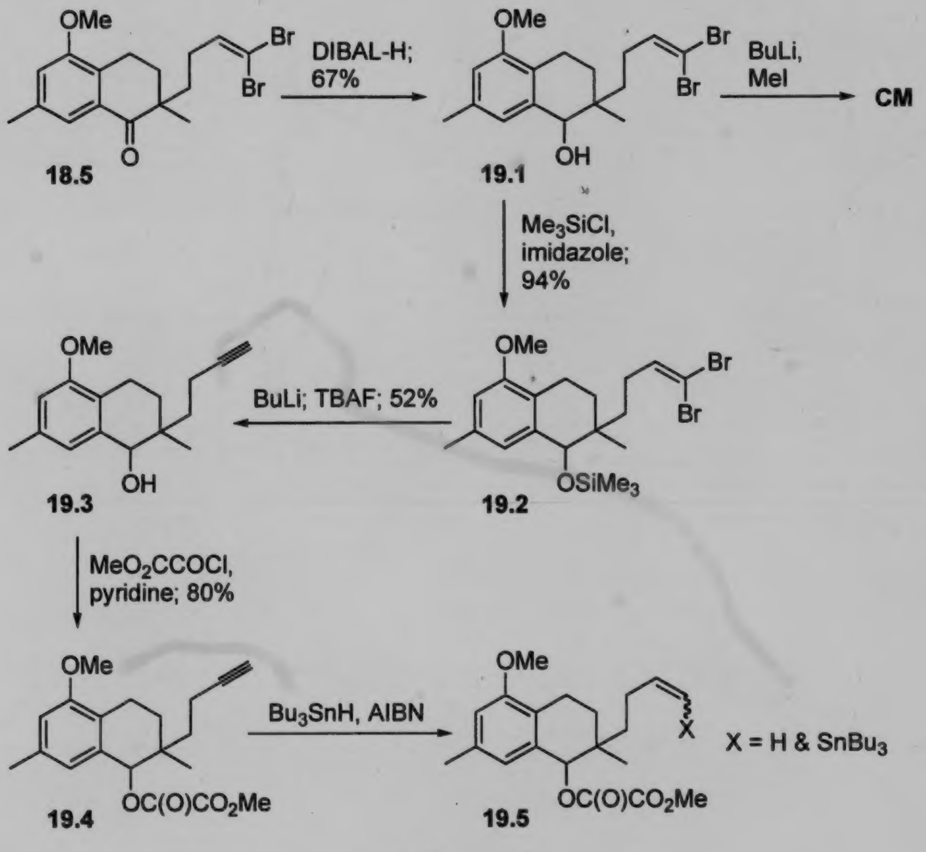
Direct alkylation of **11.2** with LDA and 5-iodopent-2-yne led only to complex mixtures (Scheme 18). However, alkylation with LDA and allyl bromide gave us **18.2** in high yield (91%).

Hydroboration of **18.2** (Scheme 18) afforded two products, the diol **18.3** (70%) and the ketone alcohol **10.3** (20%). Both **18.3** and **10.3** could be converted to dicarbonyl compound **18.4** in high yield by oxidation. Treatment of **18.4** with Ph_3P and CBr_4 in the presence of Et_3N, gave dibromide **18.5** in 98% yield.

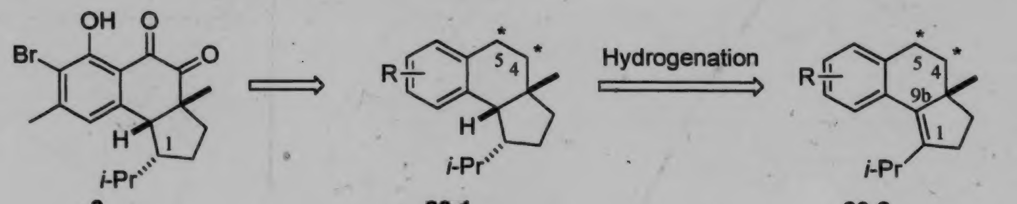


Scheme 18

Reduction of **18.5** with DIBAL-H furnished alcohol **19.1** in 67% yield (Scheme 19). Unfortunately, treatment of this alcohol with 2 equiv BuLi, followed by MeI, did not give us the desired acetylene, and only a complicated mixture was obtained. Therefore, we decided to protect the free hydroxyl before the base treatment. Accordingly, the benzylic alcohol was protected as its silyl ether (Me_3SiCl, imidazole, 94%) to give **19.2**. Treatment of this compound with 2 equiv of BuLi, followed by desilylation with Bu_4NF, afforded acetylene **19.3** in 52% yield over two steps. Compound **19.3** was then converted into the radical precursor **19.4** under standard conditions (MeO_2CCOCl, pyridine, 80%). However, treating **19.4** with Bu_3SnH and AIBN (slow addition) in PhMe at reflux did not give us any cyclized products; instead, only products (**19.5**) from the hydrostannylation of the triple bond were obtained. We did not investigate whether replacing the acetylenic hydrogen by a methyl group would have retarded the hydrostannylation sufficiently to allow generation of the desired benzylic radical.



Scheme 19

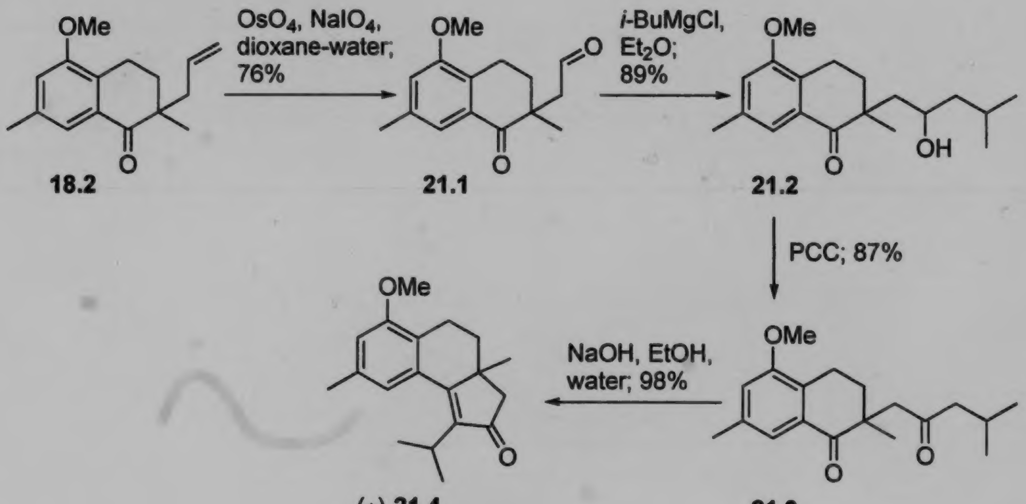


3 **20.1** **20.2**

Scheme 20

The difficulty we had encountered in establishing the stereochemistry at C(1) by radical cyclization approaches caused us to abandon radical-based methods, and we decided to pursue a new and more efficient route to our target.

As shown in Scheme 20, we realized that hamigeran B (**3**) might be easily made from intermediates such as **20.1** with all three correct stereo centers. We felt that if we could make tricyclic compound **20.2**, which bears a double bond between C(1) and C(9b), and if we could selectively reduce this double bond from the same face as the C(3a) angular methyl substituent, then we would obtain **20.1**, and eventually, our target.

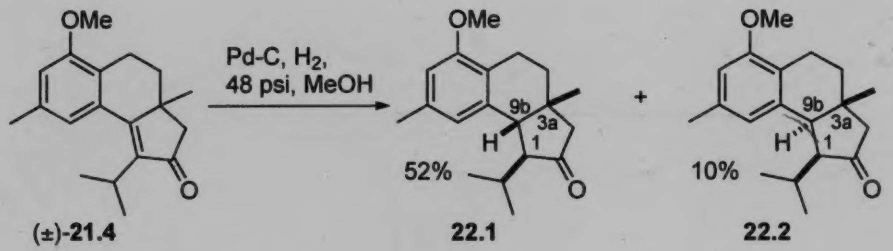


18.2 **21.1** **21.2** **21.3** **(±)-21.4**

Scheme 21

To this end, we started with compound **18.2**, one of our previous intermediates (Scheme 18). The allyl side chain of **18.2** was cleaved (Scheme 21) by the Lemieux-Johnson method[27] (OsO_4, $NaIO_4$, 76%) to afford ketone aldehyde **21.1**. The aldehyde carbonyl of this compound was selectively converted to a mixture of alcohols (**21.2**) in 89% yield by treatment with 1 equiv *i*-BuMgCl. Oxidation of this mixture, using PCC, then gave diketone **21.3** in high yield. When this diketone was boiled in aqueous ethanolic sodium hydroxide, the key intermediate enone (±)-**21.4** was generated in excellent yield (98%).

With enone (±)-**21.4** in hand, our efforts were now directed to the task of hydrogenating the carbon-carbon double bond from the same face as the angular methyl group at C(3a).



Scheme 22

Hydrogenation of ketone (±)-**21.4** over Pd-C (MeOH, H_2, 48 psi, 24 h), gave a mixture from which we could isolate ketone **22.1** as the major product in 52% yield (Scheme 22). This substance is crystalline, and single crystal X-ray analysis (Figure 2) established the structure shown in Scheme 22. The other product we isolated from the hydrogenation was ketone **22.2** (10%). The stereochemistry of this compound was tentatively assigned by extensive NMR measurements [no cross-peaks between H(9b) and the C(3a) methyl substituent].

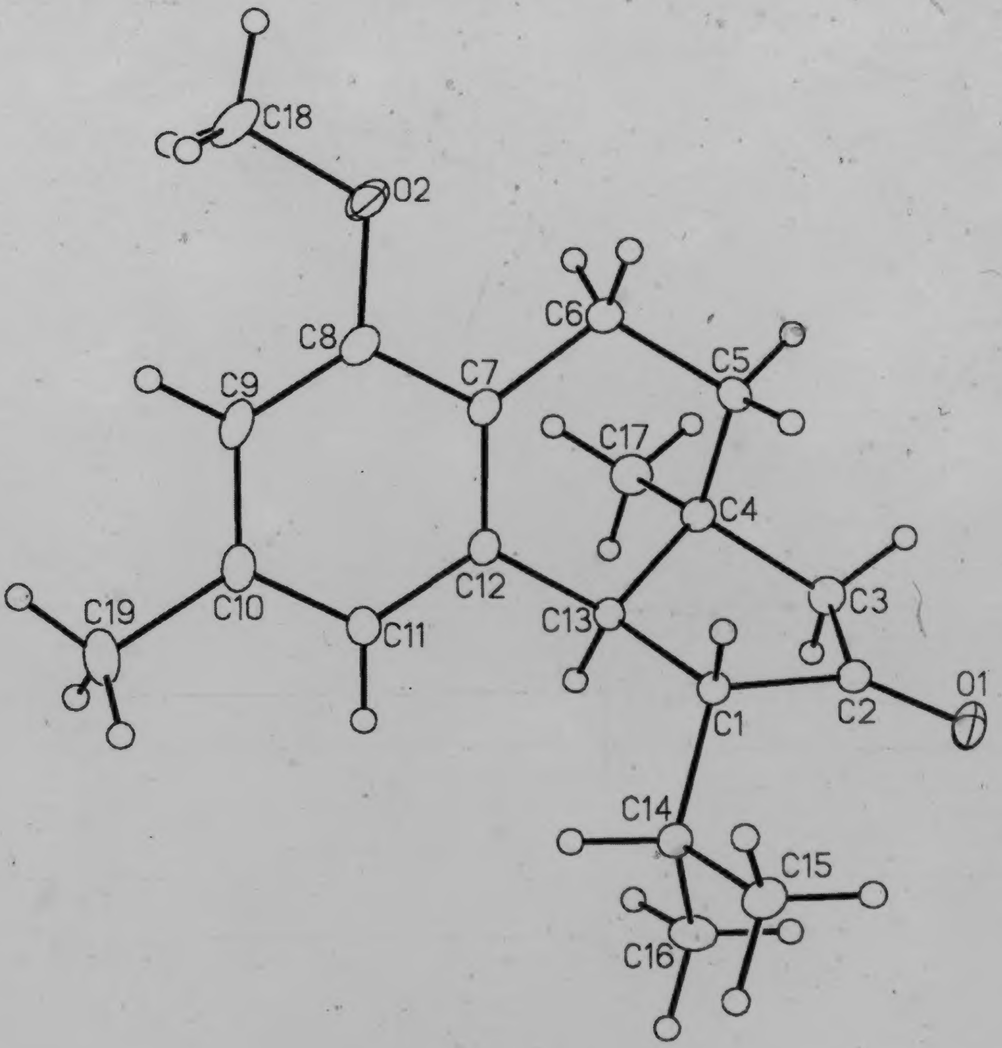
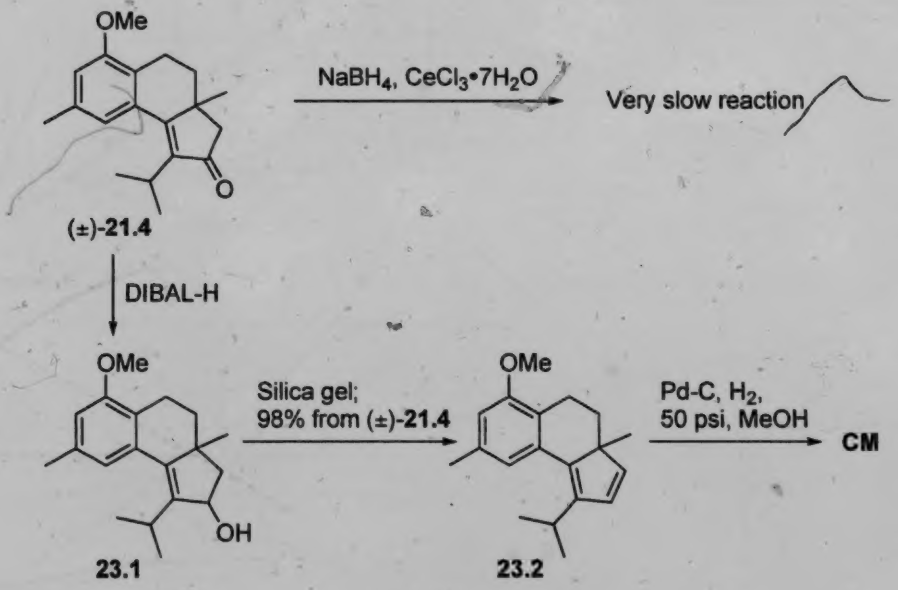


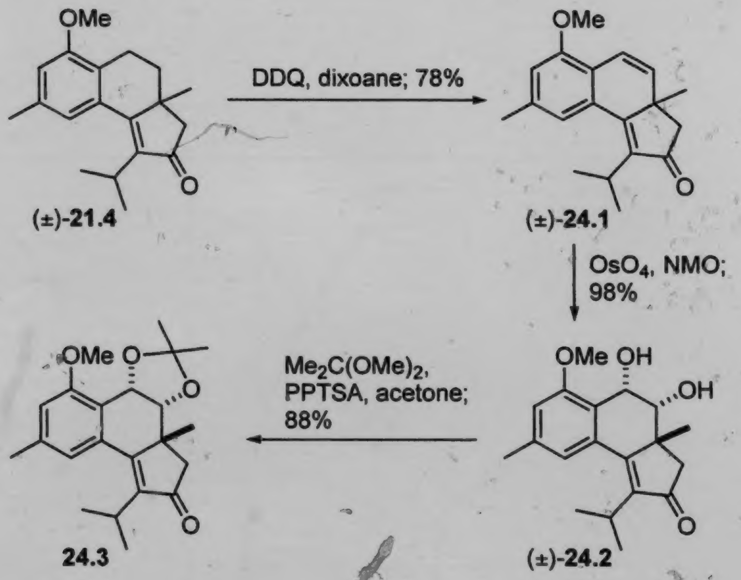
Figure 2 Crystal structure of **22.1**

As a working hypothesis, we assumed that the desired C(1) stereochemistry had indeed been generated, but that the desired product had undergone epimerization at C(1), mediated by the ketone. Consequently, we sought to block this pathway by reducing the ketone carbonyl group.



Scheme 23

Reduction of (±)-**21.4** with $NaBH_4$-$CeCl_3.7H_2O$ was extremely slow, but the ketone did react rapidly with DIBAL-H (Scheme 23). However, the resulting alcohol **23.1** is very acid sensitive, and flash chromatography over silica gel gave the corresponding elimination product, diene **23.2**. Hydrogenation of this diene (Pd-C, H_2, 50 psi, MeOH) did saturate both double bonds, but produced an inseparable mixture of stereoisomers, with the ratio of the components varying from experiment to experiment. We attributed this stereochemical outcome to a lack of facial selectivity. To enhance such selectivity during the hydrogenation, we decided to introduce bulky substituents into ketone (±)-**21.4** at C(4) and C(5) so as to block the α face of this molecule.

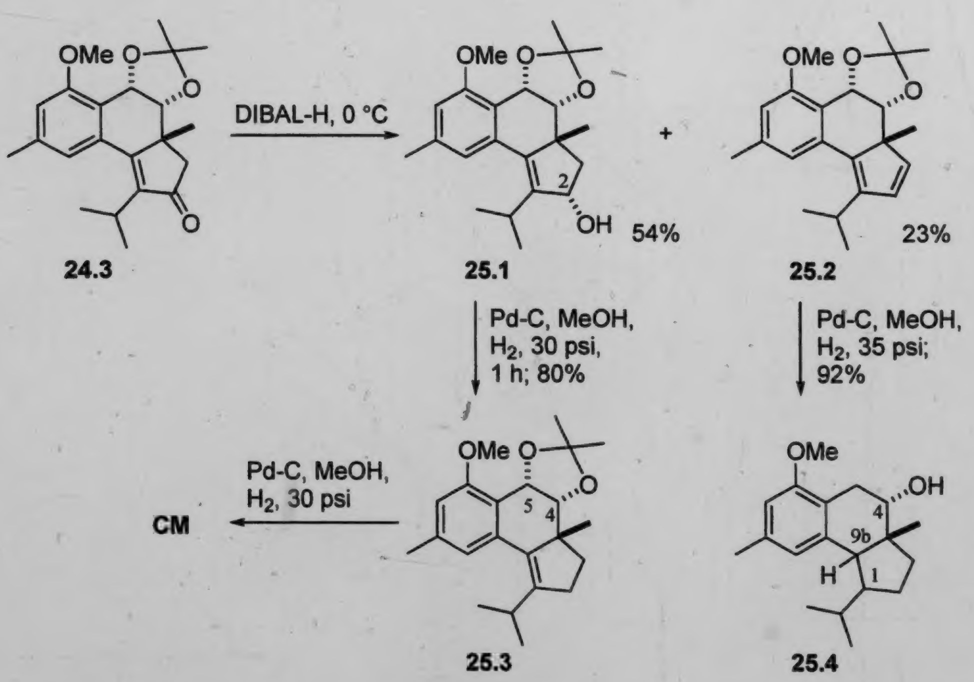


Scheme 24

Accordingly, ketone (±)-**21.4** was dehydrogenated with DDQ in dioxane at reflux, to afford compound (±)-**24.1** (78%, Scheme 24). The double bond at C(4) and C(5) was then dihydroxylated under standard conditions (catalytic OsO_4, stoichiometric NMO), and gave the expected diol [(±)-**24.2**] in excellent yield. At this point, NOE measurements showed that the hydroxyl groups were *anti* to the adjacent angular methyl group, and this assignment was later confirmed by X-ray analysis of a more advanced intermediate.

Treatment of diol (±)-**24.2** with 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate afforded the desired ketal **24.3** in 88% yield. We hoped that this ketal structure would provide sufficient bulk to block the α face of the molecule and direct hydrogenation to the opposite face.

In preparation for our planned hydrogenation studies, the carbonyl group of ketone **24.3** was reduced with DIBAL-H (Scheme 25). A 2.3:1 mixture of allylic alcohol **25.1** [tentative stereochemistry shown at C(2), assignment based on NOE measurements] and diene **25.2** was obtained.



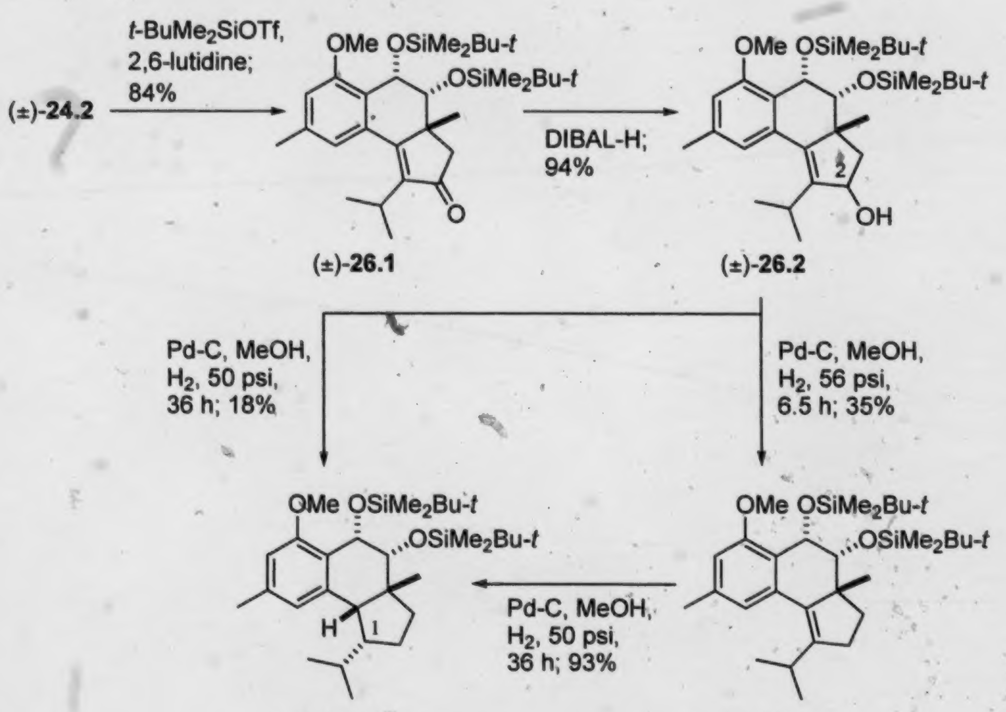
Scheme 25

Hydrogenation of allylic alcohol **25.1** at 30 psi for 1 h, gave compound **25.3** (ca 80%), resulting from hydrogenolysis of the allylic hydroxyl. However, when the reaction time was longer, only a mixture of substances lacking the benzylic oxygen originally at C(5) was formed. Hydrogenation of diene **25.2** for 36 h, under similar conditions (Pd-C, MeOH, H_2, 35 psi), gave alcohol **25.4** [stereochemistry at C(1) and C(9b) was not established] in 92% yield.

We also tried hydrogenation of diene **25.2** with other catalysts. Only the C(4)-C(5) double bond of **25.2** could be reduced with Rh-Al_2O_3 (H_2, 700 psi, 50 °C, MeOH, 19 h), Wilkinson's catalyst (H_2, 400 psi, 50 °C, MeOH, 48 h), or

Raney 2800 nickel (2800 psi, 60 °C, MeOH, 67 h). In other attempts to reduce alkene **25.3**, we found that the tetra-substituted double bond of this compound was inert to BH_3 (at room temperature) or to 9-BBN, even in THF at reflux.

From the above experiments, we concluded that only a Pd-C catalyst could successfully mediate the hydrogenation of the tetra-substituted double bond between C(1) and C(9b); but this catalyst also caused hydrogenolysis of the C(5) oxygen function of **25.2**. These observations forced us to make another modification to our hydrogenation route, so as to avoid hydrogenolysis.



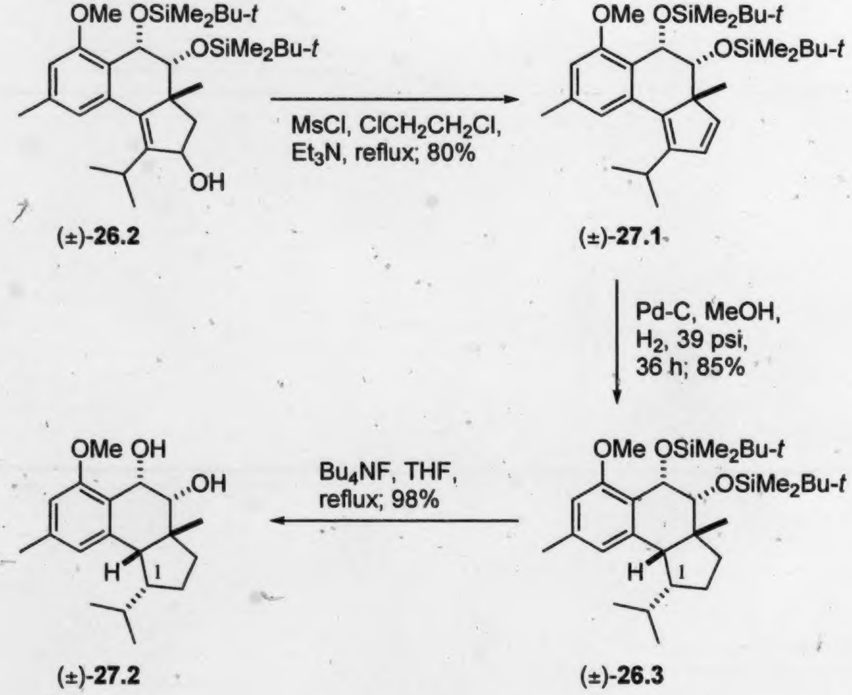
Scheme 26

We decided to protect the hydroxyl groups of (±)-**24.2** as *t*-butyldimethylsilyl ethers, which we hoped would have sufficient bulk to suppress coordination of the benzylic oxygen to the catalyst. Later, from the literature we learnt that hydrogenolysis is facilitated by the development of a partial positive charge on the benzylic carbon[28] and siloxy groups have a lowered ability to stabilize an adjacent positive charge.[29] Diol (±)-**24.2** was treated with excess $t\text{-BuMe}_2\text{SiOSO}_2\text{CF}_3$ in the presence of 2,6-lutidine to afford ketone (±)-**26.1** in 84% yield (Scheme 26). As before, this ketone was then reduced with DIBAL-H to give alcohol (±)-**26.2** (94%) as the only product, whose stereochemistry at C(2) was not established.

From our previous hydrogenation experiments, we realized that a prolonged time is required to saturate the tetrasubstituted C(1)-C(9b) double bond. The hydrogenation of alcohol (±)-**26.2** was first done for 36 h (Pd-C, H_2, 50 psi). Unfortunately, from the reaction mixture we were only able to isolate 18% of a single compound with the expected polarity on TLC plates for the desired product. The spectral data [^1H, ^{13}C NMR and MS (electrospray)] showed that this compound is indeed the product of saturation of the double bond of (±)-**26.2**. From NOE measurements, we could also observe the key cross-peaks between protons at C(1), C(9b) and the C(3a) methyl group. Based on these measurements, we determined that we had the desired product [(±)-**26.3**] from hydrogenation of (±)-**26.2**; our structure assignment to (±)-**26.3** was also later proved by single crystal X-ray analysis on the product of desilylation [(±)-**27.2**, Figure 3].

Although we could isolate the desired product, the yield was unacceptably low. On the assumption that a longer reaction time might lead to side reactions and reduce the amount of the desired product, we intentionally stopped the hydrogenation at 6.5 h; this time alkene (±)-

26.4 was isolated from the reaction mixture in 35% yield. We then hydrogenated this alkene (Pd-C, H_2, 50 psi, MeOH, 36 h), and this time we obtained the desired product [(±)-**26.3**] in excellent yield (93%).



Scheme 27

These observations suggested that the hydroxyl group at C(2) of alcohol (±)-**26.2** had a deleterious effect on the course of the hydrogenation. Although we did not know the reason for this effect, we decided to remove the hydroxyl group before the hydrogenation step.

Accordingly, alcohol (±)-**26.2** was dehydrated (Scheme 27) by mesylation conducted first at room temperature, and then at reflux in 1,2-dichloroethane, to give diene (±)-**27.1**. As expected, this diene could be hydrogenated as before (Pd-C, MeOH and H_2, 39 psi, 36 h) to afford (±)-**26.3** in high (85%) yield. Removal of the two silyl protecting groups failed with Bu_4NF at room temperature (the starting material was recovered), probably due to steric factors. However, the desilylation was successful with Bu_4NF in THF at reflux for 20 h, to give diol (±)-**27.2** (98%). This diol is a crystalline solid and so we were able to get an X-ray analysis (Figure 3), and confirm that we had the desired stereochemistry.

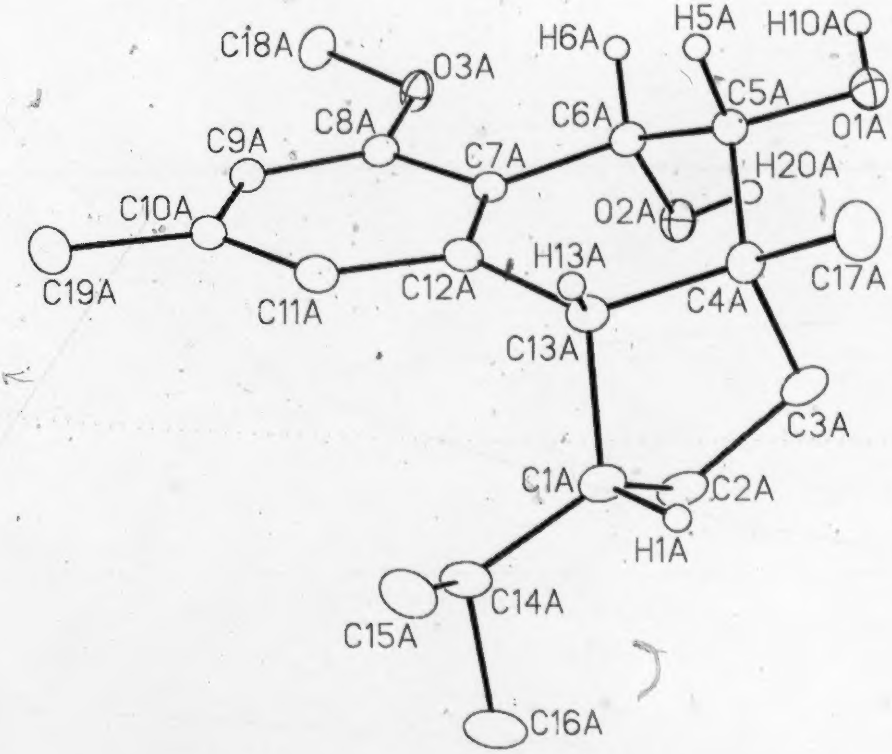
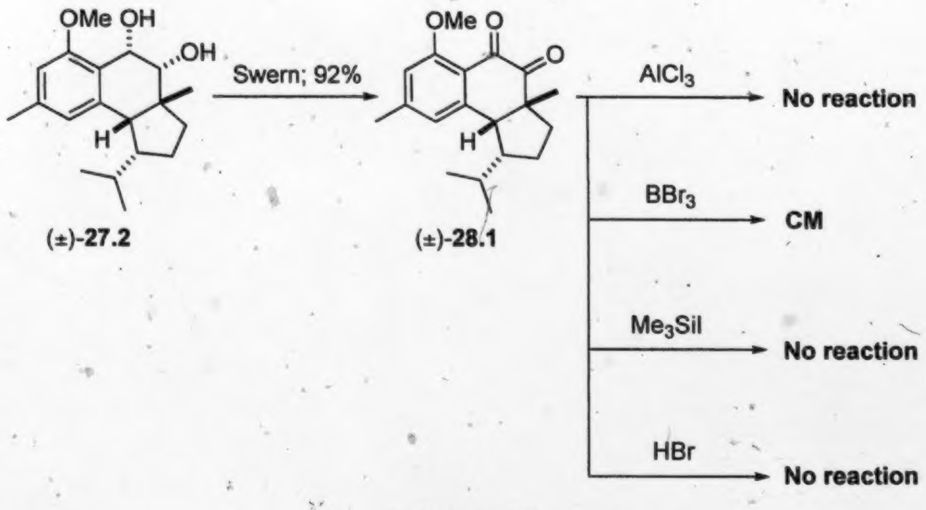
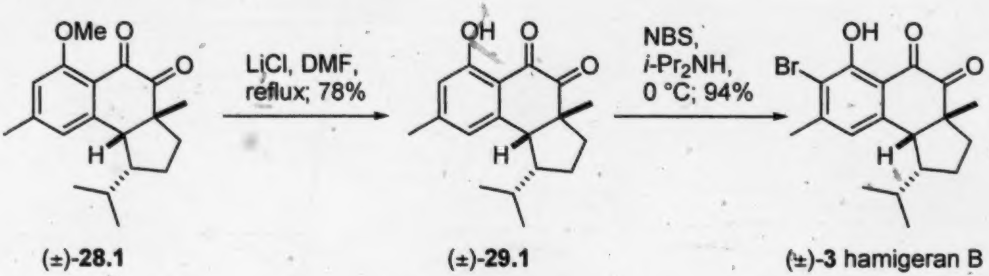


Figure 3 Crystal structure of (±)-**27.2**



Scheme 28

As shown in Scheme 28, Swern oxidation of (±)-**27.2** took the route as far as diketone (±)-**28.1** (92%). Now the stage had been set to remove of the *O*-methyl group. To our surprise, this step was troublesome. We first tried BBr_3, as Nicolaou used this method successfully (his work now having been published),[5] but only a complicated mixture was obtained. Upon treatment with other Lewis acids, such as $AlCl_3$ and Me_3SiI, even in CH_2Cl_2 at reflux, no trace of the desired product was detected. Similarly, treatment with HBr also led to no reaction.

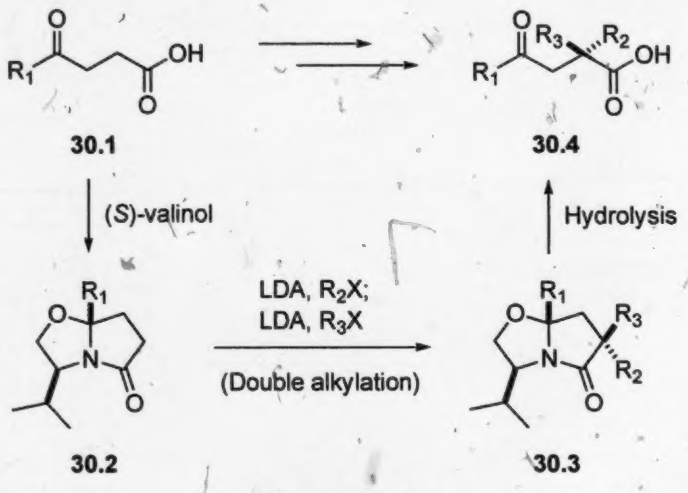


Scheme 29

Fortunately, we soon found that the demethylation of (±)-**28.1** could be done smoothly by treatment with LiCl[30] in DMF at reflux for 20 h to afford phenol (±)-**29.1** (Scheme 29). Finally, selective bromination at the *ortho* position to the phenolic hydroxyl,[26] by treatment with NBS in the presence of a catalytic amount of *i*-Pr_2NH, gave us (±)-hamigeran B [(±)-**3**, 94%]. The ^1H and ^{13}C NMR, FTIR, and mass spectral characteristics of our synthetic material [(±)-**3**] matched those reported for the natural product.[2]

2.3 Synthesis of Natural (-)-Hamigeran B.

With racemic hamigeran B in hand, our next mission was to find a way to make optically pure material. Examination of our synthesis showed immediately that the above route could be applied if we could make the key intermediate **21.4** (Scheme 21) in enantiomerically pure form, because all other stereogenic centers in the target were determined by the stereochemistry at C(3a).



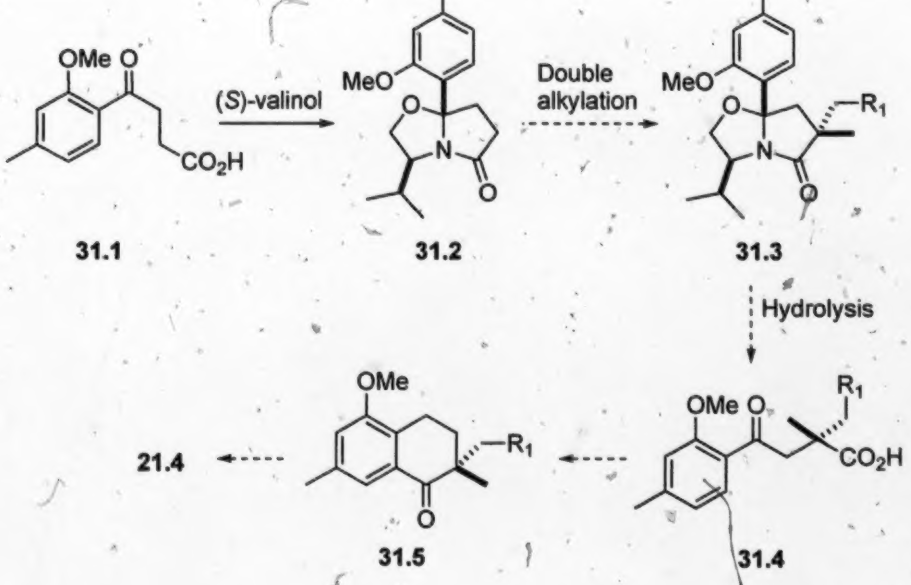
Scheme 30

To build up a system with an asymmetric quaternary carbon, we decided to use Meyers' method[31] based on lactam **30.2** (Scheme 30), because this lactam can be easily made optically pure from commercial (*S*)-valinol (**30.1** → **30.2**). This lactam favors *endo* alkylation (**30.2** → **30.3**); both enantiomers of the hydrolysis product **30.4** are accessible by switching the order of addition of the alkylating reagents and, most importantly, in most cases, diastereomers from the alkylation are separable by simple flash chromatography.

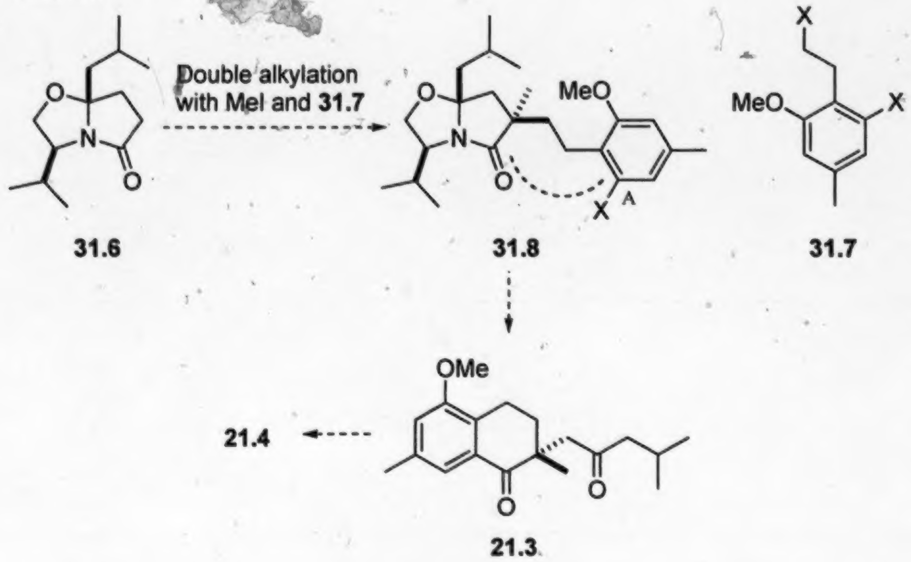
In order to apply Meyers' methodology in our synthesis, we could start from keto acid **31.1**. This was in fact easily made from acid **9.2**. Acid **31.1** was converted into lactam **31.2** by condensation with (*S*)-valinol (Scheme 31, plan A). We hoped that this lactam could be dialkylated, first with MeI, and then with a side chain bearing some functional groups which would be manipulated later on, to give **31.3**. Hydrolysis of this dialkylated lactam should afford keto acid **31.4**, and this acid would be converted into tetralone **31.5**. The tetralone represents an advanced intermediate leading to optically pure ketone **21.4**.

Alternatively, we could make lactam **31.6** (Scheme 31, plan B). This lactam would be dialkylated with MeI and the aromatic piece **31.7** to furnish **31.8**. At this stage, if we could generate a carbanion at position A on the aromatic ring, then the anion should attack the lactam carbonyl and, after hydrolysis, optically pure **21.3** should be formed. This would be condensed to the required ketone **21.4** as before (Scheme 21). Obviously, plan B looks more attractive to us because it is shorter.

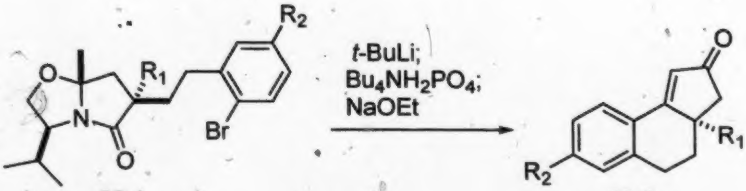
Plan A:



Plan B:



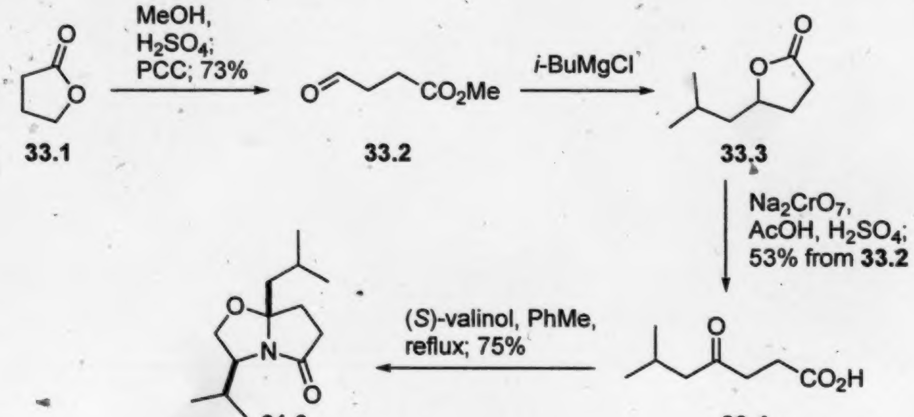
Scheme 31



32.1 **32.2**

Scheme 32

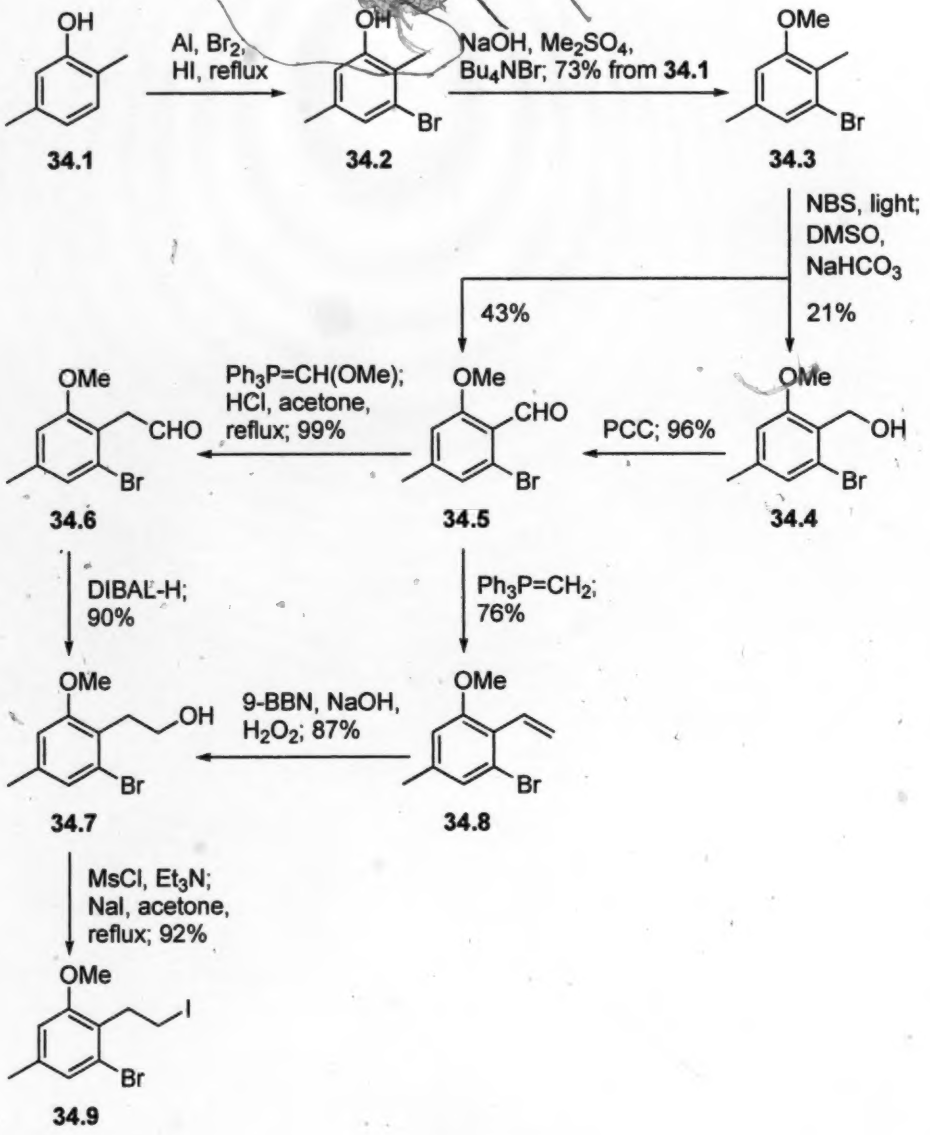
When we searched the literature, it turned out that we are not the first to conceive of this approach. In their 1993 paper,[32] Snyder and Meyers described such a one-pot sequence: upon treatment with *t*-BuLi at -78 °C, refluxing with $Bu_4NH_2PO_4$ buffer, and then refluxing with aqueous ethanolic NaOH, dialkylated lactam **32.1** could be converted into optically pure enone **32.2** in high yield (Scheme 32).



33.1 **33.2** **33.3** **31.6** **33.4**

Scheme 33

In our case, the required lactam (**31.6**) could be made as shown in Scheme 33: γ-butyrolactone **33.1** was converted into the ester aldehyde **33.2** by methanolysis and oxidation with PCC (73%).[33] Reaction of the aldehyde carbonyl group with 1 equiv of *i*-BuMgCl gave lactone **33.3** directly, and oxidation of this lactone under acidic conditions[34] afforded the keto acid **33.4** in 53% overall yield from lactone **33.2**. Finally, condensation of acid **33.4** with freshly-made (*S*)-valinol[35] in PhMe at reflux,[36] with a Dean-Stark apparatus, gave us lactam **31.6** in 75% yield. In this series only the final lactam was obtained pure, all the precursors were used crude.

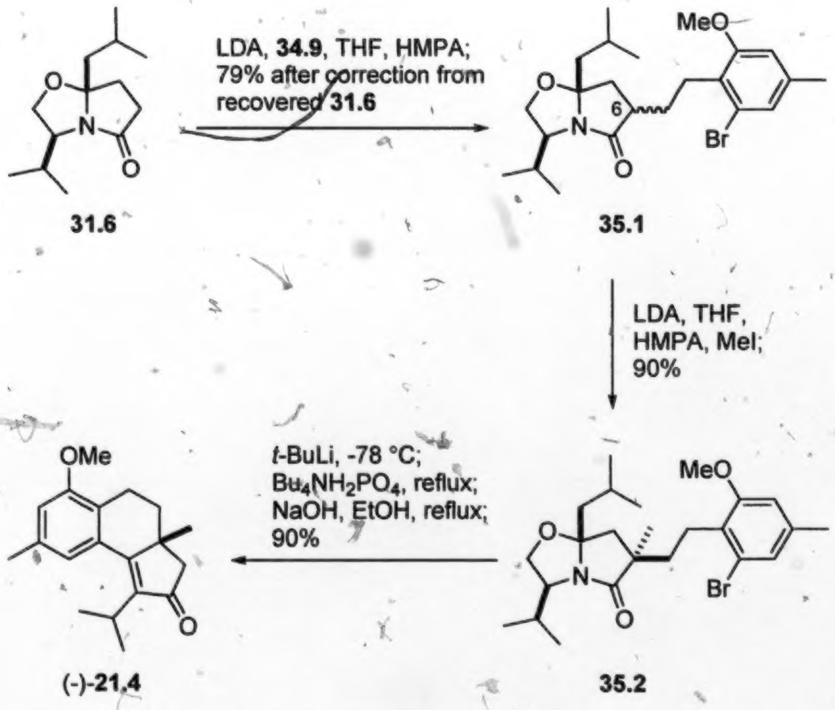


Scheme 34

To make the required aromatic piece, we started from 2,5-dimethylphenol (**34.1**). It was treated with Al and Br_2,[37] the *ortho* and *para* bromines were then removed by heating with HI[38] to give **34.2** (Scheme 34). The phenolic hydroxyl was protected as its methyl ether under standard conditions (**34.2** → **34.3**, Me_2SO_4, Bu_4NBr, NaOH, 73%). Then the more hindered methyl group of **34.3** was selectively brominated[39] (NBS, light) and oxidized[40] (DMSO and $NaHCO_3$), to give a mixture of alcohol **34.4** (21%) and aldehyde **34.5** (43%). Alcohol **34.4** could be converted into aldehyde **34.5** by simple PCC oxidation (96%).

Wittig homologation of aldehyde **34.5** with $Ph_3P{=}CH_2(OMe)$, followed by hydrolysis with hydrochloric acid in acetone, afforded aldehyde **34.6** in high yield. DIBAL-H reduction of this aldehyde gave alcohol **34.7** (90%), and the alcohol was converted into the desired iodide **34.9** by first mesylation and then treatment with NaI in acetone at reflux (92% overall). The intermediate alcohol **34.7** could also be prepared by Wittig olefination of aldehyde **34.5** (**34.5** → **34.8**, 76%) and subsequent hydroboration of **34.8** (9-BBN, NaOH, H_2O_2, 87%).

Although the reaction was slow, the two subunits — lactam **31.6** and iodide **34.9** — were successfully joined (Scheme 35) by deprotonation of the former (1.4 equiv LDA, THF, -78 °C) and addition of HMPA and then the iodide **34.9**. The mixture was left at room temperature for 36 h, and the monoalkylated product **35.1** could then be isolated by flash chromatography in 79% yield [corrected for recovered lactam **31.6** (30%)].



Scheme 35

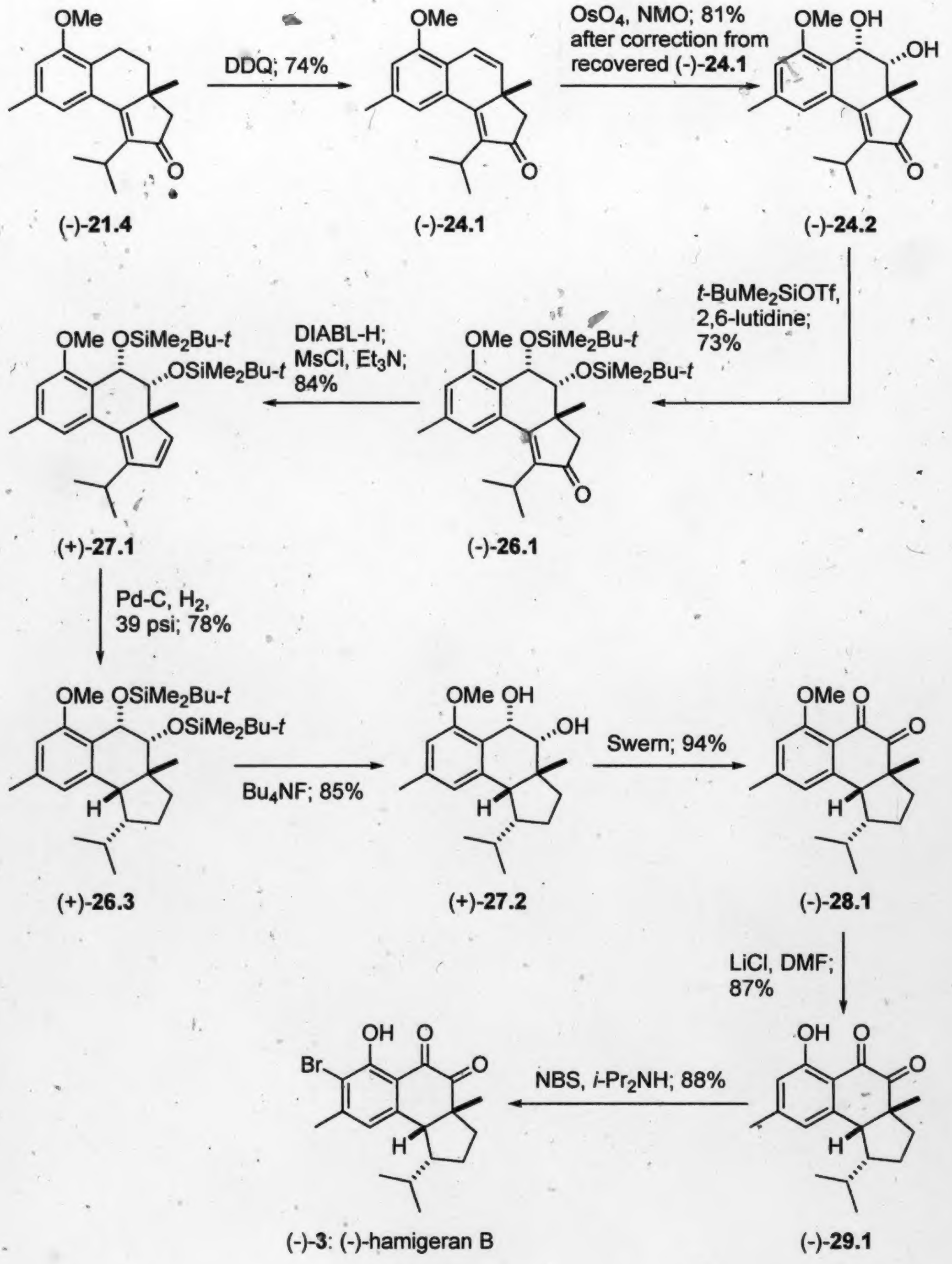
As expected, **35.1** was obtained as a mixture of C(6) epimers. We did not bother to separate them at this stage because we still needed to install a methyl group at this center. Treatment of **35.1** with LDA at -78 °C, and addition of HMPA and MeI, then gave an 18:1 mixture of the desired dialkylated lactam **35.2** (*endo* alkylation product, 90%) and its C(6) epimer (*exo* alkylation product). These two diastereomers could be separated easily by flash chromatography, so that **35.2** was obtained pure (90% yield).

With the dialkylated lactam **35.2** in hand, we now applied to this material the Meyers' benzindenone methodology:[32] treatment of **35.2** with *t*-BuLi at -78 °C, followed first by refluxing with an aqueous solution of $Bu_4NH_2PO_4$ (1.0 M) for 24 h, and then with ethanolic aqueous NaOH, brought about a cascade of reactions, ultimately affording compound (-)-**21.4** in 90% overall yield. Because lactam **35.2**, obtained from optically pure (*S*)-valinol, was itself a single compound, we assume that (-)-**21.4** is also optically pure. This assumption was confirmed later by HPLC analysis of an advanced intermediate [(+)-**27.2**, Scheme 36] on a chiral column.

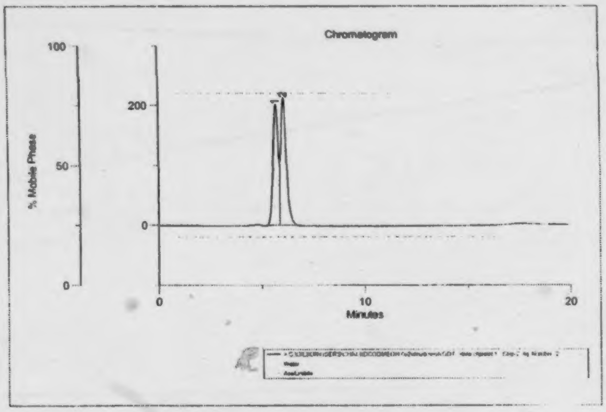
From this point, completion of the synthesis of (-)-hamigeran B [(-)-**3**] followed the method used earlier with racemic compounds, as shown in Scheme 36.

Enone (-)-**21.4** was desaturated with DDQ as before (74%), then subjected to vicinal dihydroxylation (OsO_4, NMO, 81%), and silylated [(-)-**21.4** → (-)-**24.1** → (-)-**24.2** → (-)-**26.1**]. Again, DIBAL-H reduction of ketone (-)-**26.1**, followed by dehydration via the derived mesylate, gave the expected diene (+)-**27.1**. The critical hydrogenation required a longer time than in the racemic series (possibly, the catalyst was less active), but still successfully saturated both double bonds and took the route to (+)-**26.3**.

The silicon protecting groups were then removed in the usual way (Bu_4NF, THF, at reflux, 85%), the resulting diol (+)-**27.2** was examined by HPLC on a chiral OD column (Figure 4). Although baseline separation of the corresponding racemic material [diol (±)-**27.2**, Scheme 27] was not possible, the trace for our optically active material showed no sign of a shoulder, and we judged the compound to be optically pure. This judgment was also based on the fact that our material was derived from optically pure lactam **31.6**.

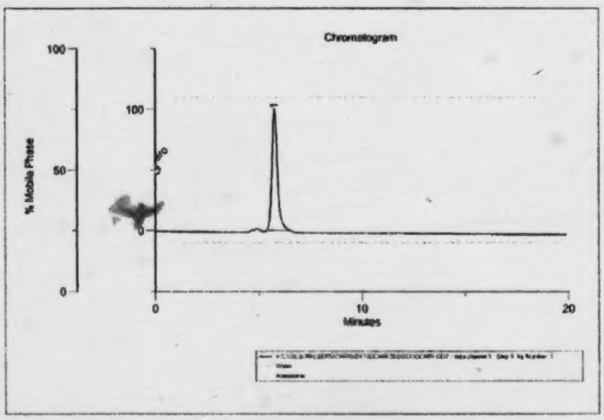

OMe
DDQ; 74%
OMe
OsO4, NMO; 81%
after correction from
recovered (-)-24.1
OMe OH
OH
O
(-)-21.4
O
(-)-24.1
O
(-)-24.2
t-BuMe2SiOTf,
2,6-lutidine;
73%
OMe OSiMe2Bu-t
OSiMe2Bu-t
DIABL-H;
MsCl, Et3N;
84%
OMe OSiMe2Bu-t
OSiMe2Bu-t
O
(+)-27.1
(-)-26.1
Pd-C, H2,
39 psi; 78%
OMe OSiMe2Bu-t
OSiMe2Bu-t
H
Bu4NF; 85%
OMe OH
OH
H
Swern; 94%
OMe O
O
H
(+)-26.3
(+)-27.2
(-)-28.1
LiCl, DMF;
87%
OH O
Br
O
H
NBS, i-Pr2NH; 88%
OH O
O
H
(-)-3: (-)-hamigeran B
(-)-29.1

Scheme 36



	Inj. Number	Peak Name	R. Time	Area	Sample Descrip.			
1	2.00	1	5.68	2372199.75	Step 2			
2	2.00	2	6.07	2725546.75	Step 2			

HPLC of (±)-**27.2**



	Inj. Number	Peak Name	R. Time	Area	Sample Descrip.			
1	1.00	1	5.76	1227145.12	Step 1			

HPLC of (+)-**27.2**

HPLC conditions:

Column: Chiralcel OD (0.46x5 cm);
Eluent: 4:1 *i*-PrOH – hexane
Flow rate: 1.0 mL/min
Detector: PDA (190-320 nm)
Integrate @ 213 nm

Figure 4

Swern oxidation of diol (+)-**27.2** led to diketone (-)-**28.1** (94%), which was then demethylated with LiCl to afford phenol (-)-**29.1** in 87% yield. Finally, regioselective bromination of the phenol (NBS, *i*-Pr_2NH, 88%) then afforded (-)-hamigeran B [(-)-**3**].

Our synthetic material had $[\alpha]_D$ -176° (*c* 0.142, CH_2Cl_2), which has the same sign and a slightly higher value than the reported specific rotation of this natural product $[\alpha]_D$ -151.5° (*c* 0.15, CH_2Cl_2)].[2] Therefore, our synthesis, the earlier synthesis by the Nicolaou group, and the recent synthesis by the Trost group, all confirm the absolute configuration of hamigeran B, which had originally been assigned by analogy to that determined for hamigeran A (**1**).

2.4 Conclusion.

Our radical cyclization approach to hamigeran B (**3**) gave the wrong stereochemistry at C(1), and led to 1-*epi*-hamigeran (**5.5**). However, we then successfully developed the hydrogenation route to make the natural product in both racemic and optically pure forms.

Our route to hamigeran B provided the second method for making this compound. This route should also work to generate some other members of the hamigeran family, such as 4-bromo-hamigeran B (**4**) and hamigeran A (**1**), by slight modification of the steps, but we did not try these possibilities.

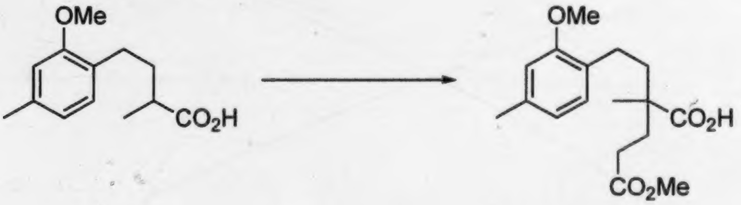
Compare to Nicolaou's synthesis (24 steps, 1.7% overall yield) and Trost's synthesis (15 steps, 10% overall yield), our synthetic route – both racemic and optically pure material – involves very simple reactions and high overall yields were obtained (20 steps, 7.4% overall yield for the synthesis of (±)-hamigeran B; 16 steps, 9.2% overall yield for the synthesis of (-)-hamigeran B). This feature should make the route amenable to scale-up. Steric factors were utilized to enforce facial selectivity and to protect a benzylic carbon-oxygen bond against hydrogenolysis. Although several examples are known in which a benzylic silyl ether survives hydrogenation of di-, tri-, and tetrasubstituted double bonds, the reports describe such experiments without commenting on the possible role of the silicon protecting group.

III Experimental Section

General Procedures.

The same general procedures were used as described in Chapter 1 of this thesis. In many ^{1}H NMR spectra, certain spin systems are described as AB even though the value of $\Delta\nu/J$ is greater than 10. Strictly speaking, such spectra should be described as AM systems.

4-(Methoxycarbonyl)-2-[(2-methoxy-4-methylphenyl)-ethyl]-2-methylbutanoic Acid (9.6).

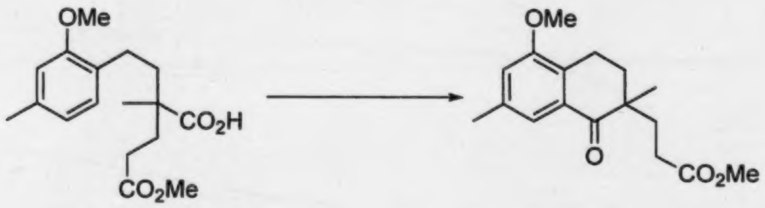


9.5 **9.6**

n-BuLi (2.5 M in hexane, 3.50 mL, 8.75 mmol) was added over ca. 10 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (1.30 mL, 9.18 mmol) in THF (20 mL). Stirring at -78 °C was continued for 30 min and then a solution of acid **9.5** (0.88 g, 3.95 mmol) in THF (5 mL) was added dropwise over ca. 15 min. After addition, stirring was continued at -78 °C for 1.5 h, and at room temperature (reaction flask transferred to water bath at room temperature) for 1.5 h, and at 50 °C (oil bath) for 2 h. The reaction mixture was then cooled to -78 °C and methyl acrylate (0.42 mL, 4.62 mmol) was added dropwise over ca. 5 min. The cooling bath was left in place but not recharged, and stirring was continued for 12 h. The reaction mixture was diluted with

Et_2O (30 mL), quenched by addition of hydrochloric acid (10%, 30 mL), and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with hydrochloric acid (10%), water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 35 cm), using 1:4 EtOAc-hexane, containing 1% AcOH, gave acid **9.6** (0.55 g, 46%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3400-2400 (broad), 2951, 1738, 1699, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (s, 3 H), 1.70-1.95 (m, 3 H), 2.01-2.11 (m, 1 H), 2.31 (s, 3 H), 2.36-2.42 (m, 2 H), 2.46-2.62 (m, 2 H), 3.66 (s, 3 H), 3.78 (s, 3 H), 6.63 (s, 1 H), 6.67 (ddd, *J* = 0.7, 1.5, 8.1 Hz, 1 H), 6.98 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.2 (q), 21.4 (q), 24.9 (t), 29.5 (t), 32.9 (t), 38.8 (t), 45.1 (s), 51.6 (q), 55.1 (q), 111.2 (d), 120.9 (d), 127.0 (s), 129.4 (d), 137.0 (s), 157.1 (s), 173.8 (s), 182.2 (s); exact mass *m/z* calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1624.

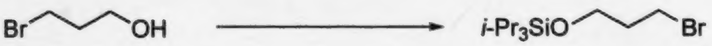
3-(5-Methoxy-2,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propionic Acid Methyl Ester (9.7).



9.6 **9.7**

$POCl_3$ (0.50 mL, 5.40 mmol) was added over ca. 2 min to a stirred and heated (140 °C) solution of acid **9.6** (1.0 g, 3.24 mmol) in $Cl_2CHCHCl_2$ (10 mL). The resulting mixture was heated at 140 °C for 5 h, cooled to room temperature, slowly quenched by addition of saturated aqueous $NaHCO_3$ (15 mL), and then extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:9 EtOAc-hexane, gave **9.7** (0.55 g, 58%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 2935, 1738, 1681, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.16 (s, 3 H), 1.82-2.04 (m, 4 H), 2.17-2.41 (m, 2 H), 2.33 (s, 3 H), 2.72-2.92 (m, 2 H), 3.60 (s, 3 H), 3.80 (s, 3 H), 6.80 (d, *J* = 0.6 Hz, 1 H), 7.42 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.8 (t), 21.5 (q), 21.7 (q), 29.2 (t), 31.4 (t), 33.3 (t), 43.7 (s), 51.5 (q), 55.5 (q), 115.1 (d), 119.6 (d), 129.1 (s), 132.0 (s), 136.8 (s), 156.6 (s), 174.1 (s), 202.1 (s); exact mass *m/z* calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1508.

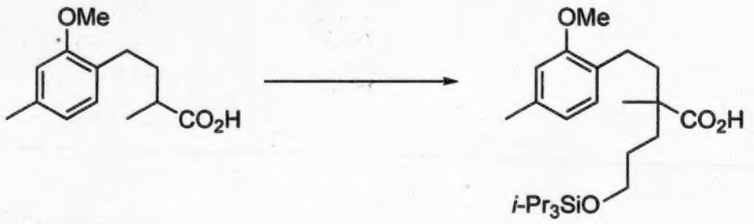
(3-Bromopropoxy)triisopropylsilane (10.1).



10.1

i-Pr_2NEt (1.9 mL, 10.9 mmol) was added in one portion to a stirred and cooled (0 °C) solution of 3-bromopropan-1-ol (0.99 g, 6.8 mmol) in CH_2Cl_2 (20 mL). *i*-Pr_3SiOTf (2.0 mL, 7.2 mmol) was then added dropwise over ca. 5 min. The ice-bath was removed and the mixture was stirred for 4.5 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:32 EtOAc-hexane, gave **10.1** (1.86 g, 93%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2943, 2892, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98-1.10 (m, 21 H), 2.02-2.09 (m, 2 H), 3.54 (t, J = 6.5 Hz, 2 H), 3.82 (t, J = 5.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 12.0 (d), 18.1 (q), 30.8 (t), 35.9 (t), 60.8 (t); exact mass *m/z* calcd for $C_9H_{20}{}^{81}BrOSi$ ($M - C_3H_7$) 253.0446, found 253.0442.

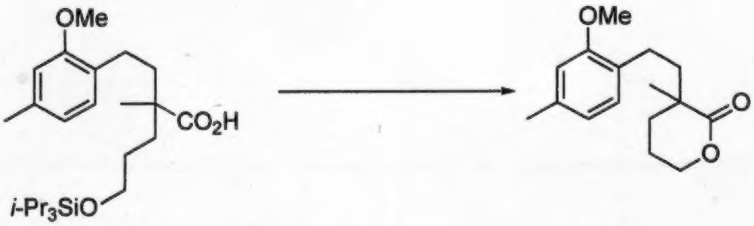
2-[2-(2-Methoxy-4-methylphenyl)ethyl]-2-methyl-5-(triisopropylsilanyloxy)pentanoic acid (10.2).



9.5 **10.2**

n-BuLi (2.5 M in hexane, 6.30 mL, 15.75 mmol) was added over ca. 10 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (2.30 mL, 16.41 mmol) in THF (20 mL). Stirring at -78 °C was continued for 30 min and a solution of acid **9.5** (1.59 g, 7.14 mmol) in THF (10 mL) was added dropwise over ca. 15 min. After addition, stirring was continued at -78 °C for 1.5 h, at room temperature for 1.5 h (mixture transferred to water bath at room temperature), and at 50 °C (oil bath) for 2 h. The reaction mixture was then cooled to -78 °C and a solution of bromide **10.1** (2.80 g, 9.50 mmol) in THF (5 mL) was added over ca. 5 min. The cooling bath was left in place but not recharged, and stirring was continued for 12 h. The reaction mixture was quenched by addition of hydrochloric acid (10%, 30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with hydrochloric acid (10%), water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 35 cm), using 1:9 EtOAc-hexane, containing 1% AcOH, gave acid **10.2** [1.41 g, 63% corrected for recovered **9.5** (0.45 g)] as a colorless oil: FTIR ($CDCl_3$ cast) 2942, 1698, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95-1.10 (m, 21 H), 1.22 (s, 3 H), 1.43-1.64 (m, 3 H), 1.68-1.76 (m, 2 H), 1.86 (dt, J = 4.7, 12.6 Hz, 1 H), 2.30 (s, 3 H), 2.48 (dt, J = 4.6, 12.7 Hz, 1 H), 2.58 (dt, J = 5.0, 12.7 Hz, 1 H), 3.60-3.70 (m, 2 H), 3.78 (s, 3 H), 6.62 (s, 1 H), 6.66 (td, J = 0.8, 7.5 Hz, 1 H), 6.98 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 12.1 (d), 18.1 (q), 21.4 (q), 21.5 (q), 25.1 (t), 28.1 (t), 34.9 (t), 39.2 (t), 45.6 (t), 55.2 (q), 63.7 (s), 111.2 (d), 120.9 (d), 127.5 (s), 129.4 (d), 136.8 (s), 157.1 (s), 182.4 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{44}NaO_4Si$ (M + Na) 459.2907, found 459.2907.

3-[2-(2-Methoxy-4-methylphenyl)ethyl]-3-methyltetrahydropyran-2-one (10.4).

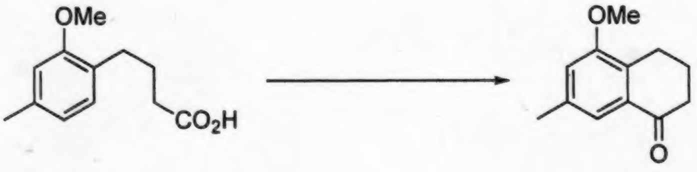


10.2 **10.4**

$POCl_3$ (0.05 mL, 0.54 mmol) was added over ca. 2 min to a stirred and heated (130 °C) solution of **10.2** (0.10 g, 0.23 mmol) in $Cl_2CHCHCl_2$ (1 mL). The mixture was heated at 135

°C for 4 h, cooled to room temperature, slowly quenched by addition of saturated aqueous $NaHCO_3$ (5 mL) and then extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 1:9 EtOAc-hexane, gave **10.4** (54 mg, 89%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.33 (s, 3 H), 1.66-1.79 (m, 2 H), 1.87-2.05 (m, 4 H), 2.28 (s, 3 H), 2.50 (dt, *J* = 4.9, 12.8 Hz, 1 H), 2.62 (dt, *J* = 4.7, 12.8 Hz, 1 H), 3.80 (s, 3 H), 4.29-4.38 (m, 2 H), 6.63 (s, 1 H), 6.68 (d, *J* = 7.5 Hz, 1 H), 6.99 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.9 (t), 21.5 (q), 24.8 (t), 26.3 (q), 32.1 (t), 40.5 (t), 42.6 (t), 55.3 (q), 70.3 (s), 111.2 (d), 121.0 (d), 127.0 (s), 129.5 (d), 137.0 (s), 157.0 (s), 176.3 (s).

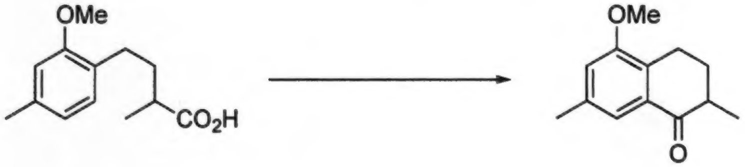
5-Methoxy-7-methyl-3,4-dihydro-2*H*-naphthalen-1-one (11.1).



9.4 **11.1**

$POCl_3$ (0.17 mL, 1.80 mmol) was added over ca. 2 min to a stirred and heated (130 °C) solution of acid **9.4** (0.31 g, 1.50 mmol) in $Cl_2CHCHCl_2$ (10 mL). The mixture was heated at 135 °C for 5 h, cooled to room temperature, slowly quenched by addition of saturated aqueous $NaHCO_3$ (10 mL), and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:32 EtOAc-hexane, gave **11.1** (0.20 g, 72%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 2998, 1759, 1684, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.06 (quin, *J* = 6.4 Hz, 2 H), 2.34 (s, 3 H), 2.58 (t, *J* = 6.9 Hz, 2 H), 2.82 (t, *J* = 6.1 Hz, 2 H), 3.80 (s, 3 H), 6.82 (s, 1 H), 7.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 21.4 (q), 22.5 (t), 22.6 (t), 38.9 (t), 55.6 (q), 115.5 (d), 118.8 (d), 130.7 (s), 133.3 (s), 136.6 (s), 156.7 (s), 198.8 (s); exact mass *m/z* calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0997.

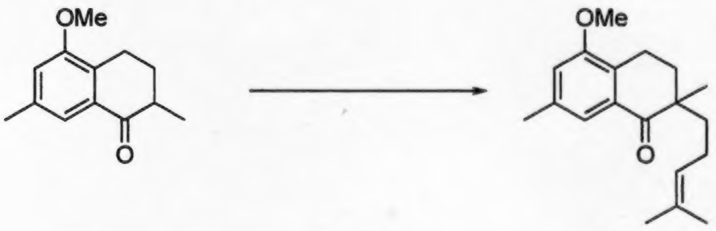
5-Methoxy-2,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (11.2).



9.5 **11.2**

$POCl_3$ (0.95 mL, 10.1 mmol) was added over ca. 2 min to a stirred and heated (135 °C) solution of acid **9.5** (1.87 g, 8.4 mmol) in $Cl_2CHCHCl_2$ (37 mL). The mixture was heated at 135 °C for 5 h, cooled to room temperature, slowly quenched by addition of saturated aqueous $NaHCO_3$ (50 mL), and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 30 cm), using 1:32 EtOAc-hexane, gave ketone **11.2** (1.43 g, 83%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 2931, 1684, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20 (d, J = 6.7 Hz, 3 H), 1.72-1.82 (m, 1 H), 2.12-2.18 (m, 1 H), 2.35 (s, 3 H), 2.48-2.56 (m, 1 H), 2.63-2.72 (m, 1 H), 3.00 (td, J = 4.4, 17.6 Hz, 1 H), 3.80 (s, 3 H), 6.80 (d, J = 0.9 Hz, 1 H), 7.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 15.3 (q), 21.4 (q), 21.9 (t), 30.7 (t), 42.1 (d), 55.6 (q), 115.1 (d), 119.0 (d), 130.3 (s), 133.1 (s), 136.6 (s), 156.7 (s), 201.2 (s); exact mass m/z calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1154.

5-Methoxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-3,4-dihydro-2*H*-naphthalen-1-one (11.3).

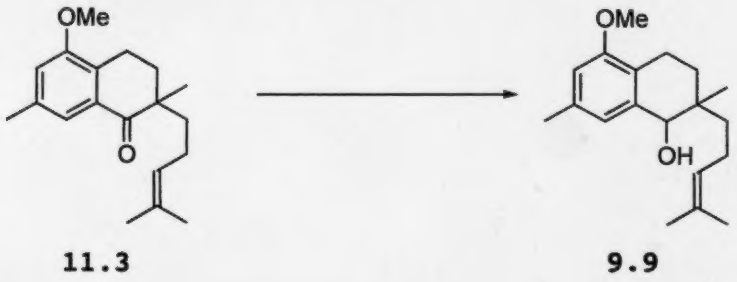


11.2 **11.3**

t-BuOK (1.73 g, 14.67 mmol) was added in one portion to a stirred solution of ketone **11.2** (1.00 g, 4.89 mmol) and 5-iodo-2-methyl-2-pentene (3.08 g, 14.67 mmol) in PhMe (40 mL). The resulting mixture was heated at reflux (oil bath at 115 °C) for 48 h, cooled to room temperature, quenched by addition of hydrochloric acid (10%, 50 mL), and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 1:32 EtOAc-hexane, gave ketone **11.3** [0.73 g, 80% corrected for recovered **11.2** (0.35 g)] as a pale yellow oil: FTIR (CH_2Cl_2 cast) 2961, 2928, 1740, 1681, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15 (s, 3

H), 1.45-1.53 (m, 1 H), 1.54 (s, 3 H), 1.57-1.64 (m, 1 H), 1.61 (s, 3 H), 1.84-1.92 (m, 2 H), 1.94-2.00 (m, 1 H), 2.01-2.07 (m, 1 H), 2.33 (s, 3 H), 2.80 (t, *J* = 6.3 Hz, 2 H), 3.83 (s, 3 H), 5.01-5.06 (m, 1 H), 6.79 (d, *J* = 1.1 Hz, 1 H), 7.41 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 17.6 (q), 18.9 (t), 21.5 (q), 21.9 (q), 22.7 (t), 25.6 (q), 33.2 (t), 36.2 (t), 44.3 (s), 55.5 (q), 114.9 (d), 119.6 (d), 124.3 (d), 129.3 (s), 131.6 (s), 132.3 (s), 136.7 (s), 156.6 (s), 202.9 (s); exact mass *m/z* calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1936.

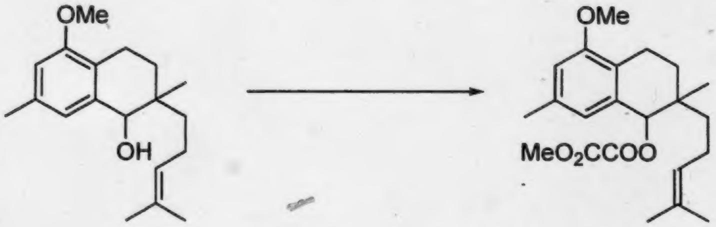
5-Methoxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-1,2,3,4-tetrahydronaphthalen-1-ol (9.9).



DIBAL-H (1.0 M, 5.0 mL, 5.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ketone **11.3** (0.50 g, 1.75 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 2 h at 0 °C, and $Na_2SO_4.10H_2O$ (1.0 g) was added. The cooling bath was removed and stirring was continued for 30 min. The mixture was then filtered through a Celite pad (2.5 x 1 cm), using CH_2Cl_2 (20 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 25 cm), using 1:99 EtOAc-hexane, gave alcohol **9.9** (0.39 g, 78%) as a colorless oil: FTIR ($CDCl_3$ cast) 3424, 2928, 1613, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ

0.88 (s, 3 H), 1.26-1.34 (m, 1 H), 1.42-1.52 (m, 3 H), 1.62 (s, 3 H), 1.66 (s, 3 H), 1.76-1.83 (m, 1 H), 1.97-2.12 (m, 2 H), 2.31 (s, 3 H), 2.45-2.53 (m, 1 H), 2.65 (td, *J* = 5.6, 12.5 Hz, 1 H), 3.80 (s, 3 H), 4.22 (s, 1 H), 5.10-5.16 (m, 1 H), 6.53 (d, *J* = 0.6 Hz, 1 H), 6.79 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 17.7 (q), 20.0 (t), 21.2 (q), 21.6 (q), 22.1 (t), 25.8 (q), 29.0 (s), 35.9 (t), 36.3 (t), 55.3 (q), 75.8 (d), 109.8 (d), 121.7 (d), 121.9 (s), 125.1 (d), 131.1 (s), 136.4 (s), 139.0 (s), 156.8 (s); exact mass *m/z* calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2088.

Oxalic Acid 5-Methoxy-2,7-dimethyl-2-(4-methylpent-3-enyl)-1,2,3,4-tetrahydronaphthalen-1-yl Methyl Ester (12.1).

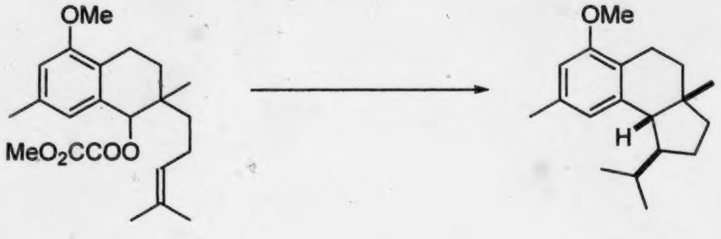


9.9 **12.1**

Pyridine (50 μL, 0.62 mmol), followed by MeO_2CCOCl (60 μL, 0.62 mmol), were added to a stirred solution of alcohol **9.9** (120 mg, 0.42 mmol) in CH_2Cl_2 (8 mL). Stirring was continued for 3 h, water (5 mL) was added to quench the reaction and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:19 EtOAc-hexane, gave ester **12.1** (144 mg, 93%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2933, 1769, 1741, 1614, 1587 cm^{-1}; ^{1}H NMR

($CDCl_3$, 500 MHz) δ 0.88 (s, 3 H), 1.29-1.36 (m, 1 H), 1.40-1.47 (m, 1 H), 1.56-1.63 (m, 1 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.90-2.04 (m, 3 H), 2.27 (s, 3 H), 2.46-2.56 (m, 1 H), 2.78 (ddd, *J* = 3.0, 6.0, 18.3 Hz, 1 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 5.03-5.08 (m, 1 H), 5.80 (d, *J* = 0.8 Hz, 1 H), 6.60 (d, *J* = 0.8 Hz, 1 H), 6.76 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 17.5 (q), 19.7 (t), 19.9 (q), 21.4 (q), 21.9 (t), 25.6 (q), 28.6 (s), 35.5 (t), 37.5 (t), 53.3 (q), 55.2 (q), 79.5 (d), 111.0 (d), 122.8 (d), 124.5 (d), 131.4 (s), 133.5 (s), 136.6 (s), 156.9 (s), 157.5 (s), 158.4 (s); exact mass *m/z* calcd for $C_{22}H_{30}O_5$ 374.2093, found 374.2091.

(1*R,3a*R**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene (12.2).**

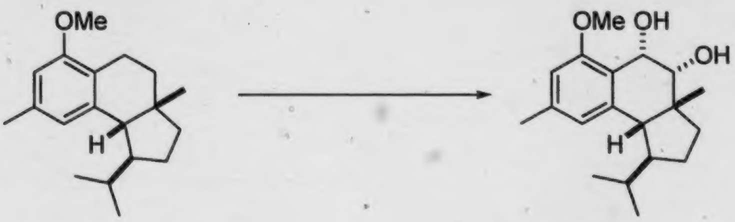


12.1 **12.2**

A solution of Bu_3SnH (1.8 mL, 6.69 mmol) and AIBN (50 mg, 0.30 mmol) in PhH (20 mL) was injected over ca. 15 h to a stirred and refluxing (oil bath at 85 °C) solution of ester **12.1** (1.01 g, 2.70 mmol) in PhH (100 mL). Stirring was continued for 3 h at 85 °C after the addition. The mixture was cooled and the solvent was concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:49 EtOAc-hexane, gave compound **12.2** (0.65 g, 89%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2950, 1612, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (d, *J* = 6.9 Hz, 3 H), 0.97

(d, *J* = 6.7 Hz, 3 H), 0.98 (s, 3 H), 1.29-1.36 (m, 1 H), 1.42-1.49 (m, 2 H), 1.57-1.66 (m, 2 H), 1.70-1.79 (m, 2 H), 1.93-2.01 (m, 1 H), 2.29 (d, *J* = 10.2 Hz, 1 H), 2.31 (s, 3 H), 2.58-2.66 (m, 2 H), 3.79 (s, 3 H), 6.60 (d, *J* = 0.8 Hz, 1 H), 6.76 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.3 (q), 19.8 (t), 21.6 (q), 21.9 (t), 22.8 (q), 26.3 (q), 27.1 (d), 32.0 (t), 39.3 (t), 40.3 (s), 51.7 (d), 54.0 (d), 55.2 (q), 108.1 (d), 121.6 (s), 122.5 (d), 135.0 (s), 141.3 (s), 156.8 (s); exact mass *m/z* calcd for $C_{19}H_{28}O$ 272.2140, found 272.2136.

(1*R,3a*S**,4*S**,5*R**,9b*S**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-diol (15.3) via intermediates (15.1) and (15.2).**

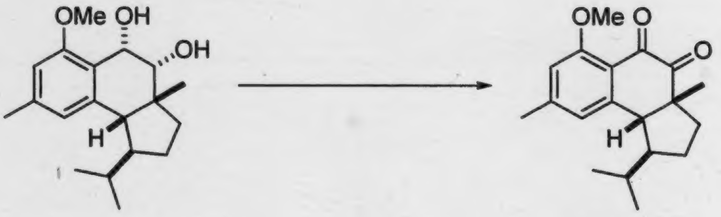


12.2 **15.3**

NBS (0.42 g, 2.35 mmol) was added to a stirred solution of **12.2** (0.61 g, 2.24 mmol) in CCl_4 (30 mL) and the stirred solution was irradiated (standard Pyrex apparatus) with UV light (Hanovia lamp type 30620) at 10 °C for 1 h (the flask was irradiated from the top while immersed in an ice-water bath). DBU (0.5 mL, 3.27 mmol) was then added and the mixture was stirred for 6 h. Water (20 mL) was added and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:19 EtOAc-hexane, gave a colorless oil, which was a mixture of the starting material and the desired olefin **15.2** (2.6:1 by ^{1}H NMR).

OsO_4 (4 mg) and NMO (0.37 g, 3.10 mmol) were added to a stirred solution of the above material in a mixture of water (2 mL), *t*-BuOH (3 mL), CCl_4 (10 mL), and acetone (20 mL) (the solvents were added in any order to the starting material.) Stirring was continued for 12 h. Water (20 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:9 to 1:2 EtOAc-hexane, gave diol **15.3** [0.11 g, 56% corrected for recovered **12.2** (0.43 g)] as a colorless oil: FTIR (CH_2Cl_2 cast) 3434, 2954, 1680, 1610, 1586 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 1.09 (s, 3 H), 1.39-1.49 (m, 2 H), 1.70-1.77 (m, 1 H), 1.91-1.98 (m, 1 H), 2.04-2.12 (m, 1 H), 2.18-2.26 (m, 1 H), 2.30 (s, 3 H), 2.47 (d, *J* = 9.5 Hz, 1 H), 2.75 (s, 1 H), 3.23 (s, 1 H), 3.59 (d, *J* = 4.1 Hz, 1 H), 3.82 (s, 3 H), 5.08 (d, *J* = 4.0 Hz, 1 H), 6.55 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 15.8 (q), 21.9 (q), 23.0 (q), 24.8 (t), 27.8 (d), 28.0 (q), 35.4 (t), 44.3 (s), 52.4 (d), 55.5 (d), 56.0 (q), 66.8 (d), 75.9 (d), 108.8 (d), 120.5 (s), 122.3 (d), 138.4 (s), 141.7 (s), 157.8 (s); exact mass *m/z* calcd for $C_{19}H_{28}O_3$ 304.2039, found 304.2033.

(1*R,3a*R**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(±)-5.3].**

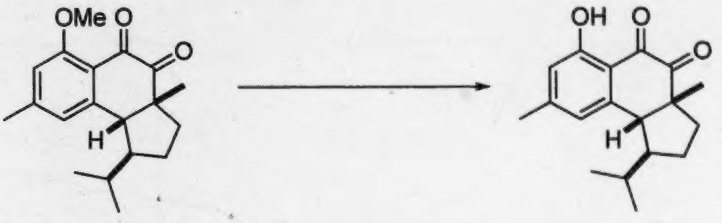


15.3 **(±)-5.3**

DMSO (0.20 mL, 2.80 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.20 mL, 2.24 mmol) in CH_2Cl_2 (7 mL). Stirring was continued for 30 min, and diol **15.3** (125 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) was added dropwise over ca. 5 min, a further portion of CH_2Cl_2 (1 mL) being used as a rinse. Stirring at -78 °C was continued for 1 h, and Et_3N (0.70 mL, 5.02 mmol) was added dropwise over ca. 2 min. Stirring was continued for 1 h, the dry-ice bath was removed, and stirring was continued for 10 h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:4 EtOAc-hexane, gave diketone (±)-**5.3** (111 mg, 90%) as yellow crystals: FTIR (CH_2Cl_2 cast) 2957, 1723, 1678, 1605, 1566 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.75 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 1.20 (s, 3 H), 1.43-1.52 (m, 2 H), 1.56-1.63 (m, 2 H), 1.65-1.72 (m, 1 H), 2.40 (s, 3 H), 2.52-2.62 (m, 1 H), 2.67 (d, *J* = 11.1 Hz, 1 H), 3.90 (s, 3 H), 6.62 (s, 1

H), 6.70 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 15.6 (q), 21.8 (q), 22.0 (t), 22.4 (q), 22.5 (q), 27.2 (d), 33.9 (t), 55.2 (d), 56.0 (q), 56.5 (s), 57.6 (d), 111.2 (d), 118.7 (s), 122.9 (d), 147.1 (s), 147.4 (s), 161.8 (s), 179.2 (s), 200.3 (s); exact mass *m/z* calcd for $C_{19}H_{24}O_3$ 300.1726, found 300.1726.

(1*R,3a*R**,9b*R**)-6-Hydroxy-1-isopropyl-3a,8-dimethyl-2,3-3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(±)-5.4].**

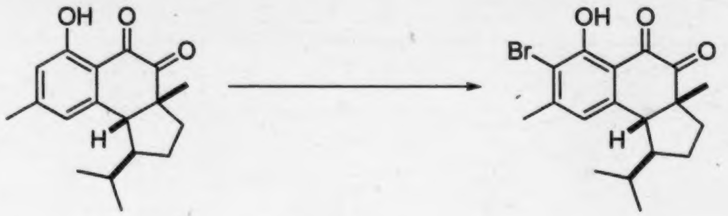


(±)-**5.3** (±)-**5.4**

$AlCl_3$ (233 mg, 1.74 mmol) was added in one portion to a stirred solution of diketone (±)-**5.3** (105 mg, 0.35 mmol) in CH_2Cl_2 (20 mL). The mixture was heated at reflux (oil bath at 40 °C) for 10 h and cooled to 0 °C. Hydrochloric acid (10%, 10 mL) was added slowly and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 3:7 EtOAc-hexane (containing 1%v/v MeOH), gave phenol (±)-**5.4** (77.6 mg, 77%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3369, 2962, 1716, 1667, 1624, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, *J* = 6.2 Hz, 3 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 1.39 (s, 3 H), 1.52-1.66 (m, 3 H), 1.71-1.78 (m, 1 H), 2.23 (ddd, *J* = 3.5, 5.7, 15.3 Hz, 1 H), 2.33-2.42 (m, 1 H), 2.40

(s, 3 H), 3.45 (s, 1 H), 6.64 (s, 1 H), 6.76 (s, 1 H), 8.60 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.1 (q), 20.3 (t), 21.6 (q), 22.6 (q), 23.0 (q), 28.2 (d), 35.0 (t), 46.3 (d), 52.4 (d), 63.6 (s), 115.0 (d), 117.5 (d), 119.0 (s), 150.4 (s), 157.49 (s), 157.54 (s), 204.0 (s), 206.9 (s); exact mass *m/z* calcd for $C_{18}H_{22}O_3$ 286.1569, found 286.1567.

(1*R,3a*R**,9b*R**)-7-Bromo-6-hydroxy-1-isopropyl-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(±)-1-*epi*-hamigeran B] [(±)-5.5].**

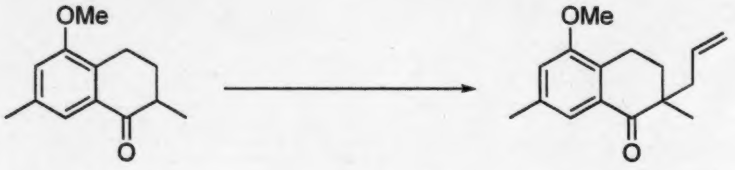


(±)-5.4 **(±)-5.5**

NBS (3.0 mg, 0.017 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise over ca. 5 min to a stirred and cooled (0 °C) solution of phenol (±)-**5.4** (4.0 mg, 0.014 mmol) and *i*-Pr_2NH (ca 0.01 mL, 0.070 mmol) in CH_2Cl_2 (2 mL). The cold bath was removed after the addition, and stirring was continued for 3.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 30 cm), using 1:3 EtOAc-hexane (containing 1%v/v MeOH), gave (±)-1-*epi*-hamigeran B [(±)-**5.5**] (5.0 mg, 98%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3326, 2962, 1717, 1669, 1616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, *J* = 6.1 Hz, 3 H), 1.10 (d, *J* = 6.1 Hz, 3 H), 1.39 (s, 3 H), 1.51-1.65 (m, 3 H), 1.72-1.79 (m, 1 H), 2.22 (ddd, *J* = 3.6, 5.7, 15.1 Hz, 1 H), 2.35-2.44 (m, 1 H), 2.51 (s, 3 H), 3.43 (s, 1 H), 6.90 (s, 1 H), 9.20

(s, 1 H); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 20.0 (q), 20.3 (t), 21.6 (q), 23.0 (q), 24.5 (q), 28.2 (d), 35.1 (t), 46.2 (d), 52.2 (d), 63.7 (s), 110.0 (s), 118.7 (d), 119.6 (s), 149.2 (s), 154.2 (s), 155.6 (s), 203.7 (s), 206.2 (s); exact mass *m/z* calcd for $C_{18}H_{21}{}^{79}BrO_3$ 364.0674, found 364.0676.

2-Allyl-5-methoxy-2,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (18.2).

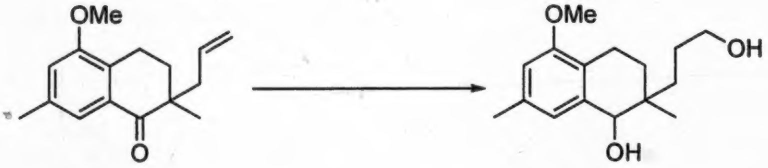


11.2 **18.2**

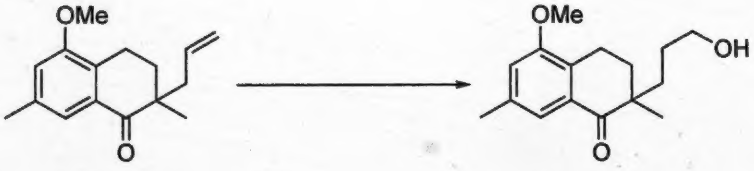
n-BuLi (2.5 M, 2.4 mL, 6.00 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.93 mL, 6.60 mmol) in THF (20 mL), and stirring at -78 °C was continued for 30 min. A solution of ketone **11.2** (1.09 g, 5.30 mmol) in THF (10 mL) was added dropwise over ca. 15 min, and stirring was continued at -78 °C for 1.5 h. Allyl bromide (0.93 mL, 10.50 mmol) was added dropwise over ca. 5 min. The cooling bath was left in place but not recharged, and stirring was continued for 12 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 30 cm), using 1:32 EtOAc-hexane, gave ketone **18.2** (1.18 g, 91%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3074, 2930, 1682, 1609 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.15 (s, 3 H), 1.80-1.88 (m, 1 H), 1.97-2.03 (m, 1 H), 2.24

(tdd, J = 1.1, 7.5, 13.7 Hz, 1 H), 2.34 (s, 3 H), 2.40 (dd, J = 7.3, 13.8 Hz, 1 H), 2.74-2.88 (m, 2 H), 3.80 (s, 3 H), 5.00-5.07 (m, 2 H), 5.73-5.81 (m, 1 H), 6.80 (d, J = 1.0 Hz, 1 H), 7.45 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.8 (t), 21.5 (q), 21.7 (q), 32.8 (t), 40.9 (t), 44.2 (s), 55.6 (q), 115.0 (d), 118.0 (t), 119.6 (d), 129.4 (s), 132.1 (s), 134.1 (d), 136.7 (s), 156.6 (s), 202.5 (s); exact mass m/z calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1465.

2-(3-Hydroxypropyl)-5-methoxy-2,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (18.3) and 2-(3-Hydroxypropyl)-5-methoxy-2,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (10.3).



18.2 **18.3**



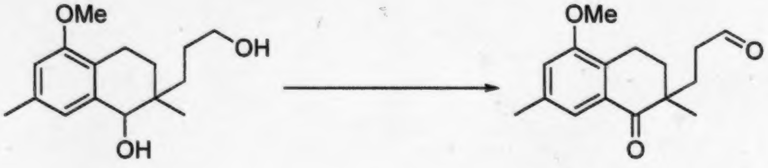
18.2 **10.3**

9-BBN (0.5 M in THF, 5.0 mL, 2.50 mmol) was added dropwise over ca. 10 min to a stirred and cooled (0 °C) solution of olefin **18.2** (0.20 g, 0.82 mmol) in THF (10 mL). The ice bath was removed and stirring was continued for 10 h. The mixture was cooled to 0 °C and quenched by successive slow addition of MeOH (1 mL), NaOH (2.0 N, 2 mL) and H_2O_2 (30%, 1 mL). The ice bath was left in place but not recharged, and stirring was continued for 2 h. The reaction mixture was then diluted with water (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:3 EtOAc-hexane, gave diol **18.3** (126 mg, 70%) and keto alcohol **10.3** (43 mg, 20%), both as colorless oils.

Diol **18.3** had: FTIR (CH_2Cl_2 cast) 3346, 2934, 1613, 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.80 (s, 3 H), 1.29-1.36 (m, 1 H), 1.42-1.48 (m, 1 H), 1.50-1.56 (m, 1 H), 1.58-1.73 (m, 4 H), 1.77-1.84 (m, 1 H), 2.31 (s, 3 H), 2.44-2.52 (m, 1 H), 2.66 (td, J = 5.4, 12.7 Hz, 1 H), 3.60-3.69 (m, 2 H), 3.79 (s, 3 H), 4.23 (s, 1 H), 6.56 (s, 1 H), 6.80 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.8 (t), 20.8 (q), 21.5 (q), 26.5 (t), 29.0 (t), 32.5 (t), 35.6 (t), 55.2 (q), 63.7 (s), 109.9 (d), 121.93 (s), 121.95 (d), 136.5 (s), 138.7 (s), 156.9 (s); exact mass (electrospray) m/z calcd for $C_{16}H_{24}NaO_3$ (M + Na) 287.1623, found 287.1624.

Keto alcohol **10.3** had: FTIR (CH_2Cl_2 cast) 3430, 2935, 1680, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (s, 3 H), 1.48-1.60 (m, 4 H), 1.68-1.75 (m, 1 H), 1.84-1.90 (m, 1 H), 1.99-2.05 (m, 1 H), 2.34 (s, 3 H), 2.75-2.88 (m, 2 H), 3.57 (t, J = 6.0 Hz, 2 H), 3.83 (s, 3 H), 6.80 (d, J = 1.0 Hz, 1 H), 7.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.9 (t), 21.5 (q), 22.1 (q), 27.4 (t), 32.5 (t), 33.1 (t), 44.0 (t), 55.6 (q), 63.1 (s), 115.1 (d), 119.6 (d), 129.3 (s), 132.1 (s), 136.8 (s), 156.6 (s), 203.0 (s); exact mass m/z calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1570.

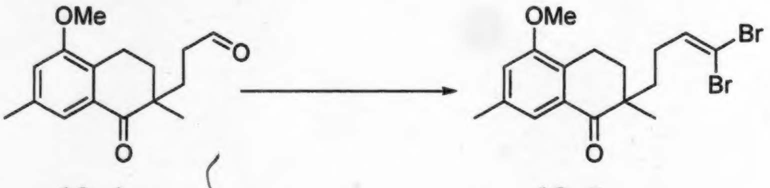
3-(5-Methoxy-2,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propionaldehyde (18.4).



18.3 **18.4**

Dry DMSO (0.85 mL, 12.00 mmol) in CH_2Cl_2 (5 mL) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.89 mL, 10.00 mmol) in CH_2Cl_2 (30 mL). Stirring was continued for 30 min, and diol **18.3** (0.70 g, 2.66 mmol) in CH_2Cl_2 (5 mL) was added dropwise over ca. 5 min, a further portion of CH_2Cl_2 (1 mL) being used as a rinse. Stirring at -78 °C was continued for 1 h, and Et_3N (2.8 mL, 20.00 mmol) was added dropwise over ca. 2 min. Stirring was continued for 1 h, the dry-ice bath was removed and stirring was continued for 10 h. Saturated aqueous NH_4Cl (40 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:9 EtOAc-hexane, gave keto aldehyde **18.4** (0.63 g, 91%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2933, 2854, 2723, 1723, 1679, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (s, 3 H), 1.83-2.03 (m, 4 H), 2.34 (s, 3 H), 2.36-2.54 (m, 2 H), 2.76-2.92 (m, 2 H), 3.81 (s, 3 H), 6.81 (d, J = 1.1 Hz, 1 H), 7.42 (d, J = 0.7 Hz, 1 H), 9.74 (t, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.8 (t), 21.5 (q), 22.0 (q), 28.6 (t), 33.4 (t), 39.1 (t), 43.6 (s), 55.6 (q), 115.2 (d), 119.5 (d), 129.1 (s), 131.9 (s), 136.9 (s), 156.6 (s), 202.0 (d), 202.2 (s); exact mass *m/z* calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1415.

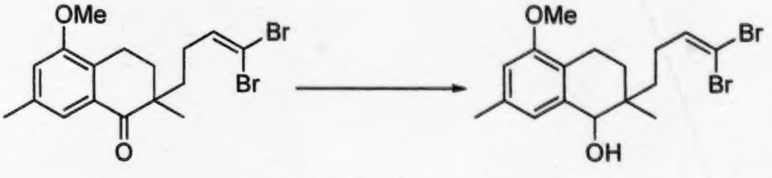
2-(4,4-Dibromobut-3-enyl)-5-methoxy-2,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (18.5).



18.4 **18.5**

Ph_3P (1.10 g, 4.82 mmol) was added to a stirred and cooled (-15 °C) solution of CBr_4 (1.40 g, 4.82 mmol) in CH_2Cl_2 (40 mL). Stirring at -15 °C was continued for 30 min and the mixture was then cooled to -78 °C. A solution of keto aldehyde **18.4** (0.83 g, 3.21 mmol) in CH_2Cl_2 (10 mL) was added dropwise over ca. 5 min, followed by Et_3N (0.71 mL, 5.10 mmol). The cooling bath was removed and stirring was continued for 30 h. Water (30 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:9 EtOAc-hexane, gave ketone **18.5** [1.07 g, 98%, corrected for recovered **18.4** (0.15 g)] as a yellow oil: FTIR (CH_2Cl_2 cast) 2932, 2854, 1681, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (s, 3 H), 1.62 (ddd, J = 5.3, 11.8, 13.7 Hz, 1 H), 1.74 (ddd, J = 5.3, 11.4, 13.7 Hz, 1 H), 1.86-1.92 (m, 1 H), 1.98-2.14 (m, 3 H), 2.35 (s, 3 H), 2.76-2.88 (m, 2 H), 3.80 (s, 3 H), 6.34 (t, J = 7.3 Hz, 1 H), 6.81 (d, J = 0.9 Hz, 1 H), 7.43 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.8 (t), 21.5 (q), 21.8 (q), 28.1 (t), 33.0 (t), 34.2 (t), 44.0 (s), 55.6 (q), 89.0 (s), 115.1 (d), 119.6 (d), 129.1 (s), 132.1 (s), 136.9 (s), 138.3 (d), 156.6 (s), 202.2 (d); exact mass *m/z* calcd for $C_{17}H_{20}{}^{81}Br_2O_2$ 417.9789, found 417.9787.

2-(4,4-Dibromobut-3-enyl)-5-methoxy-2,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (19.1).

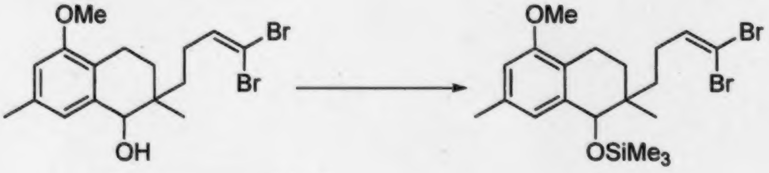


18.5 **19.1**

DIBAL-H (1 M, 3.50 mL, 3.50 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ketone **18.5** (1.04 g, 2.50 mmol) in CH_2Cl_2 (30 mL). Stirring was continued for 2 h at -78 °C and $Na_2SO_4.10H_2O$ (1.0 g) was added. The cooling bath was removed, stirring was continued for 30 min, and the mixture was filtered through a Celite pad (1 x 1.5 cm), using CH_2Cl_2 (20 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25 cm), using 1:19 EtOAc-hexane, gave alcohol **19.1** (0.70 g, 67%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3396, 2931, 2857, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (s, 3 H), 1.39 (ddd, J = 5.3, 11.7, 13.7 Hz, 1 H), 1.43-1.50 (m, 2 H), 1.59 (ddd, J = 5.6, 11.7, 13.7 Hz, 1 H), 1.80 (ddd, J = 6.5, 9.2, 13.7 Hz, 1 H), 2.11-2.24 (m, 2 H), 2.32 (s, 3 H), 2.46-2.54 (m, 1 H), 2.66 (td, J = 5.6, 18.1 Hz, 1 H), 3.80 (s, 3 H), 4.21 (s, 1 H), 6.41 (t, J = 7.2 Hz, 1 H), 6.57 (s, 1 H), 6.80 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.8 (t), 20.8 (q), 21.5

(q), 27.6 (t), 28.6 (t), 34.3 (t), 35.8 (s), 55.2 (q), 75.4 (d), 88.4 (s), 110.0 (d), 121.66 (d), 121.69 (s), 136.7 (s), 138.7 (s), 139.2 (d), 156.9 (s); exact mass *m/z* calcd for $C_{17}H_{22}{}^{81}Br_2O_2$ 419.9946, found 419.9944.

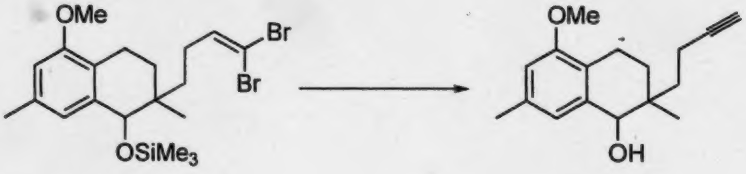
[2-(4,4-Dibromobut-3-enyl)-5-methoxy-2,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yloxy]trimethylsilane (19.2).



19.1 **19.2**

Me_3SiCl (0.15 mL, 1.16 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **19.1** (0.42 g, 1.02 mmol) and imidazole (84 mg, 1.22 mmol) in CH_2Cl_2 (20 mL). The ice bath was removed and stirring was continued for 30 min. Saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:19 EtOAc-hexane, gave **19.2** (0.47 g, 94%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2954, 2858, 1614 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.13 (s, 9 H), 0.75 (s, 3 H), 1.22-1.34 (m, 2 H), 1.50 (ddd, *J* = 5.5, 11.9, 13.4 Hz, 1 H), 1.84-2.06 (m, 3 H), 2.25 (s, 3 H), 2.71 (td, *J* = 7.5, 18.4 Hz, 1 H), 2.87 (td, *J* = 6.3, 18.4 Hz, 1 H), 3.37 (s, 3 H), 4.29 (s, 1 H), 6.05 (t, *J* = 7.2 Hz, 1 H), 6.41 (d, *J* = 0.8 Hz, 1 H), 6.86 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 1.0 (q), 20.5 (t), 21.6 (q), 21.7 (q), 28.1 (t), 29.4 (t), 34.3 (t), 36.6 (s), 54.8 (q), 77.7 (d), 88.6 (s), 109.8 (d), 122.2 (s), 122.3 (d), 135.7 (s), 139.5 (s), 139.9 (d), 157.4 (s); exact mass *m/z* calcd for $C_{20}H_{30}{}^{81}Br_2O_2Si$ 492.0341, found 492.0343.

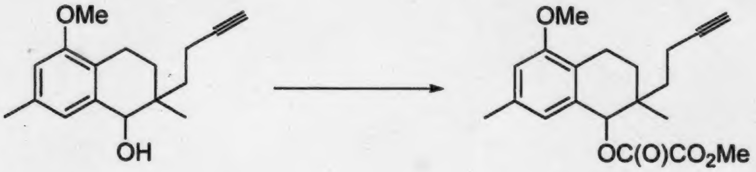
2-But-3-ynyl-5-methoxy-2,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (19.3).



19.2 **19.3**

n-BuLi (2.5 M in hexane, 0.85 mL, 2.13 mmol) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of compound **19.2** (0.45 g, 0.92 mmol) in THF (20 mL). The cooling bath was left in place but not recharged, and stirring was continued for 10 h. Saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Bu_4NF (1.0 M in THF, 1.0 mL, 1.00 mmol) was added to a stirred solution of the residue in THF (10 mL). Stirring was continued for 3 h and the solvent was concentrated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:19 EtOAc-hexane, gave acetylene **19.3** (0.12 g, 53%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3575, 3258, 2919, 2106, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 3 H), 1.42-1.49 (m, 1 H), 1.54-1.63 (m, 2 H), 1.76-1.85 (m, 2 H), 1.94 (t, *J* = 2.7 Hz, 1 H), 2.20-2.38 (m, 2 H), 2.31 (s, 3 H), 2.43-2.52 (m, 1 H), 2.64-2.73 (m, 1 H), 3.79 (s, 3 H), 4.22 (s, 1 H), 6.57 (s, 1 H), 6.79 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.0 (t), 19.8 (t), 20.5 (q), 21.5 (q), 28.6 (t), 35.8 (t), 35.9 (s), 55.2 (q), 68.0 (d), 75.0 (d), 85.4 (s), 110.0 (d), 121.7 (s), 121.9 (d), 136.6 (s), 138.6 (s), 156.9 (s); exact mass *m/z* calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1620.

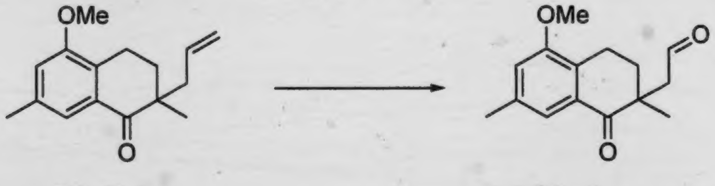
Oxalic Acid 2-But-3-ynyl-5-methoxy-2,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl Methyl Ester (19.4).



19.3 **19.4**

Pyridine (81 μL, 1.00 mmol), followed by MeO_2CCOCl (86 μL, 0.90 mmol) were added to a stirred solution of alcohol **19.3** (112 mg, 0.45 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 1.5 h and the solvent was then concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:19 EtOAc-hexane, gave ester **19.4** (123 mg, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3290, 2953, 2118, 1769, 1742, 1614 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 3 H), 1.58-1.78 (m, 3 H), 1.92 (t, *J* = 2.7 Hz, 1 H), 1.89-1.98 (m, 1 H), 2.18-2.26 (m, 2 H), 2.28 (s, 3 H), 2.46-2.57 (m, 1 H), 2.78 (ddd, *J* = 3.5, 6.6, 18.5 Hz, 1 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 5.78 (d, *J* = 0.7 Hz, 1 H), 6.61 (d, *J* = 0.7 Hz, 1 H), 6.74 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.9 (t), 19.6 (t), 19.8 (q), 21.4 (q), 28.3 (t), 35.6 (t), 36.2 (s), 53.4 (q), 55.2 (q), 68.2 (d), 79.3 (d), 84.6 (s), 111.0 (d), 122.4 (s), 122.5 (d), 133.1 (s), 136.7 (s), 156.8 (s), 157.4 (s), 158.3 (s); exact mass *m/z* calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.1624.

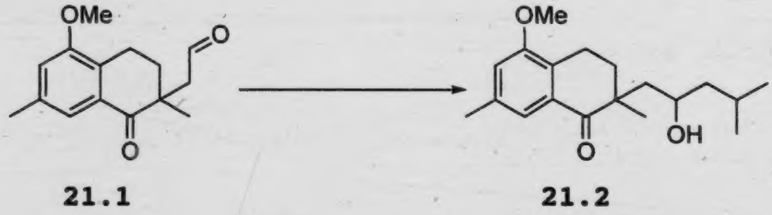
(5-Methoxy-2,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetaldehyde (21.1).



18.2 **21.1**

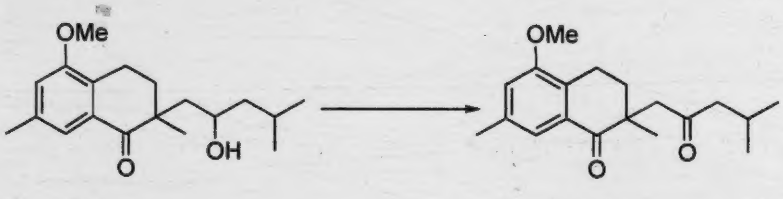
OsO_4 (4 mg) was added to a solution of ketone **18.2** (78 mg, 0.32 mmol) in dioxane-water (3:1, 10 mL). The mixture was stirred for 30 min, and $NaIO_4$ (0.21 g, 1.00 mmol) was added. Stirring was continued for 3.5 h. Water (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:19 EtOAc-hexane, gave aldehyde **21.1** (60 mg, 76%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2935, 2841, 2736, 1719, 1679, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 3 H), 1.92 (td, *J* = 4.7, 13.4 Hz, 1 H), 2.15-2.22 (m, 1 H), 2.35 (s, 3 H), 2.53 (dd, *J* = 2.5, 16.1 Hz, 1 H), 2.73-2.82 (m, 2 H), 2.94 (td, *J* = 4.7, 18.2 Hz, 1 H), 3.85 (s, 3 H), 6.81 (s, 1 H), 7.43 (s, 1 H), 9.82 (t, *J* = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.8 (t), 21.5 (q), 21.7 (q), 33.6 (t), 43.8 (t), 51.3 (s), 55.6 (q), 115.5 (d), 119.7 (d), 129.1 (s), 131.5 (s), 137.1 (s), 156.6 (s), 201.2 (s), 201.3 (d); exact mass *m/z* calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1256.

2-(2-Hydroxy-4-methylpentyl)-5-methoxy-2,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (21.2).



i-BuMgCl (2.0 M, 3.0 mL, 6.0 mmol) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of aldehyde **21.1** (1.36 g, 5.5 mmol) in Et_2O (60 mL). The mixture was stirred at -78 °C for 1 h. The cooling bath was left in place but not recharged, and stirring was continued for 10 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL), and extracted with Et_2O (3 x 60 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:19 EtOAc-hexane, gave the intermediate alcohols **21.2** (1.49 g, 89%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3443, 2954, 1676, 1608 cm^{-1}; exact mass *m/z* calcd for $C_{19}H_{28}O_3$ 304.2039, found 304.2035; both the ^1H and ^{13}C NMR spectra indicated the presence of two alcohols (ca 1:1).

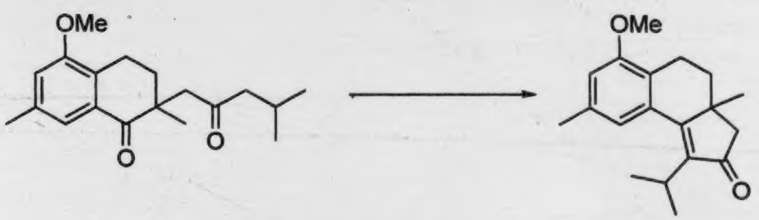
5-Methoxy-2,7-dimethyl-2-(4-methyl-2-oxopentyl)-3,4-dihydro-2*H*-naphthalen-1-one (21.3).



21.2 **21.3**

PCC (1.9 g, 8.6 mmol) was added in one portion to a stirred solution of the above alcohols in CH_2Cl_2 (60 mL). The mixture was stirred at room temperature for 3.5 h and then filtered through a Celite pad (2.5 x 3 cm). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 30 cm), using 1:9 EtOAc-hexane, gave diketone **21.3** (1.32 g, 79% over two steps) as a yellow oil: FTIR (CH_2Cl_2 cast) 2957, 1712, 1681, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, J = 6.6 Hz, 6 H), 1.22 (s, 3 H), 1.84 (ddd, J = 3.7, 5.2, 13.4 Hz, 1 H), 2.12 (septet, J = 6.6 Hz, 1 H), 2.28 (dd, J = 3.0, 6.9 Hz, 2 H), 2.37 (s, 3 H), 2.40-2.48 (m, 1 H), 2.68-2.78 (m, 1 H), 2.81 (AB q, J = 17.3 Hz, $\Delta\nu_{AB}$ = 217.4 Hz, 2 H), 2.97 (td, J = 4.5, 17.9 Hz, 1 H), 3.85 (s, 3 H), 6.84 (d, J = 1.2 Hz, 1 H), 7.50 (d, J = 0.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.8 (t), 21.6 (q), 22.2 (q), 22.7 (q), 24.8 (d), 32.5 (t), 43.5 (t), 51.3 (s), 52.7 (t), 55.7 (q), 115.2 (d), 119.7 (d), 129.1 (s), 131.9 (s), 136.7 (s), 156.5 (s), 201.5 (s), 208.5 (s); exact mass m/z calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1881.

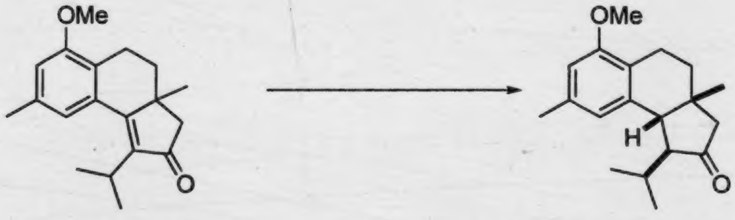
1-Isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one [(±)-21.4].



21.3 (±)-**21.4**

NaOH (50%, 5 mL) was added to a stirred solution of diketone **21.3** (0.28 g, 0.93 mmol) in EtOH (15 mL). The mixture was heated at reflux (oil bath at 80 °C) for 36 h, cooled to room temperature, neutralized with hydrochloric acid (3%, 20 mL), and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:9 EtOAc-hexane, gave enone (±)-**21.4** (0.26 g, 98%) as yellow plates: mp 105-106 °C; FTIR (CH_2Cl_2 cast) 2956, 1693, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 3 H), 1.19 (d, J = 6.9 Hz, 3 H), 1.37 (d, J = 7.0 Hz, 3 H), 1.66-1.74 (m, 1 H), 2.07 (ddd, J = 1.0, 6.9, 13.2 Hz, 1 H), 2.26 (AB q, J = 18.5 Hz, $\Delta\nu_{AB}$ = 60.8 Hz, 2 H), 2.37 (s, 3 H), 2.61-2.71 (m, 1 H), 2.86 (dd, J = 7.0, 18.8 Hz, 1 H), 3.12 (septet, J = 7.0 Hz, 1 H), 3.83 (s, 3 H), 6.70 (s, 1 H), 6.86 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.8 (q), 20.6 (q), 20.8 (t), 21.7 (q), 23.0 (q), 25.7 (d), 36.0 (t), 38.7 (t), 51.1 (s), 55.3 (q), 111.8 (d), 120.9 (d), 123.5 (s), 131.5 (s), 136.0 (s), 140.6 (s), 157.2 (s), 170.1 (s), 208.2 (s); exact mass *m/z* calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1774.

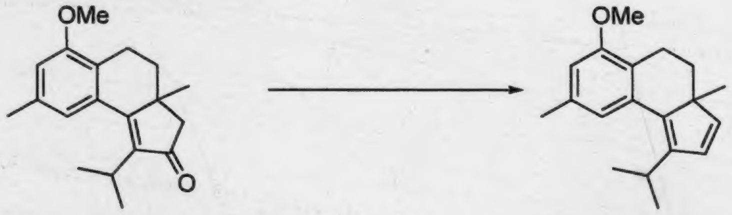
(1*R**,3a*S**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-1,3,3a,4,5,9b-hexahydrocyclopenta[*a*]naphthalene-2-one (22.1).



(±)-21.4 **22.1**

Pd-C (10%, 10 mg) was added to a solution of enone (±)-**21.4** (17.8 mg, 0.06 mmol) in MeOH (1 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (48 psi) for 9 h. The mixture was filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (5 mL) as a rinse and the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using hexane, gave ketone **22.1** (9.3 mg, 52%) as white crystals: mp 98-99 °C; FTIR (CH_2Cl_2 cast) 2956, 1735, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.0 (d, J = 6.9 Hz, 3 H), 1.09 (s, 3 H), 1.16 (d, J = 7.0 Hz, 3 H), 1.50-1.62 (m, 2 H), 2.06-2.24 (m, 4 H), 2.32 (s, 3 H), 2.46-2.55 (m, 1 H), 2.76 (d, J = 10.6 Hz, 1 H), 2.78-2.85 (m, 1 H), 3.80 (s, 3 H), 6.52 (s, 1 H), 6.55 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 16.8 (q), 19.8 (t), 21.6 (q), 21.8 (q), 23.6 (q), 27.8 (d), 30.0 (t), 34.8 (s), 48.9 (d), 55.2 (q), 55.9 (t), 61.1 (d), 108.8 (d), 120.1 (s), 122.5 (d), 135.7 (s), 138.0 (s), 157.3 (s), 219.5 (s); exact mass *m/z* calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1934.

1-Isopropyl-6-methoxy-3a,8-dimethyl-4,5-dihydro-3a*H*-cyclopenta[*a*]naphthalene (23.2).

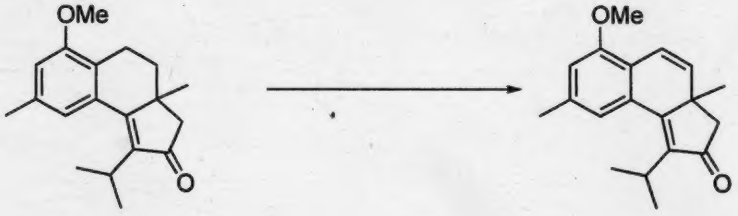


(±)-**21.4** **23.2**

DIBAL-H (1 M, 0.4 mL, 0.4 mmol) was added dropwise to a stirred and cooled (0 °C) solution of enone (±)-**21.4** (76 mg, 0.27 mmol) in CH_2Cl_2 (5 mL). After the addition, the ice-bath was removed and stirring was continued for 5 h. The mixture was cooled to 0 °C, $Na_2SO_4.10H_2O$ (0.5 g) was added, and stirring was continued for 30 min. The mixture was filtered through a Celite pad (1 x 1.5 cm), using CH_2Cl_2 as a rinse. The solvent was concentrated and the residue was dissolved in $CDCl_3$ (2 mL) and stirred for 3 h [this step was carried out because in a previous experiment conversion of the initial alcohol to the diene was observed after leaving an NMR sample overnight in $CDCl_3$]. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 1:9 EtOAc-hexane, gave diene **23.2** (71 mg, 98%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3057, 2959, 1696, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (s, 3 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 1.28 (d, *J* = 6.9 Hz, 3 H), 1.22-1.30 (m, 1 H), 2.12 (ddd, *J* = 0.8, 6.5, 11.9 Hz, 1 H), 2.36 (s, 3 H), 2.58-2.67 (m, 1 H), 2.86 (dd, *J* = 6.7, 18.2 Hz, 1 H), 3.20 (septet, *J* = 6.8 Hz, 1 H), 3.80 (s, 3 H), 6.37 (d, *J* = 5.3 Hz, 1 H), 6.46 (d, *J* = 5.3 Hz, 1 H), 6.55 (s, 1 H), 6.83 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ

17.3 (q), 21.1 (t), 21.8 (q), 22.0 (q), 22.9 (q), 26.2 (d), 31.7 (t), 52.3 (s), 55.2 (q), 108.7 (d), 119.3 (d), 121.6 (s), 129.1 (d), 133.7 (s), 135.5 (s), 142.8 (s), 143.1 (s), 145.5 (d), 157.2 (s); exact mass *m/z* calcd for $C_{19}H_{24}O$ 268.1827, found 268.1830.

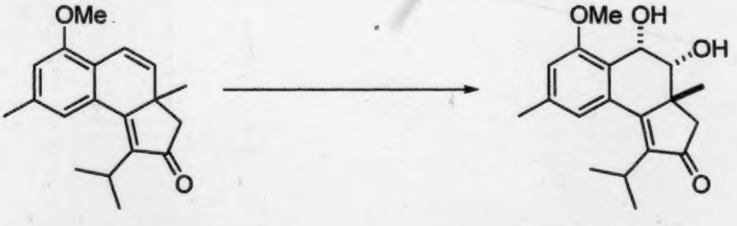
1-Isopropyl-6-methoxy-3a,8-dimethyl-3,3a-dihydrocyclopenta[*a*]naphthalen-2-one [(±)-24.1].



(±)-21.4 **(±)-24.1**

DDQ (1.20 g, 5.30 mmol) was added in one portion to a stirred solution of ketone (±)-**21.4** (1.01 g, 3.60 mmol) in 1,4-dioxane (60 mL) and the mixture was heated at reflux for 8.5 h (Ar atmosphere), cooled to room temperature, and filtered through a short pad of silica gel (5 x 3.5 cm), using Et_2O (100 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 30 cm), using 1:9 EtOAc-hexane, gave enone (±)-**24.1** (0.78 g, 78%) as a yellow oil: FTIR ($CHCl_3$ cast) 2958, 1696, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, *J* = 6.8 Hz, 3 H), 1.18 (s, 3 H), 1.36 (d, *J* = 7.1 Hz, 3 H), 2.40 (s, 3 H), 2.44 (AB q, *J* = 17.6 Hz, $\Delta\nu_{AB}$ = 109.1 Hz, 2 H), 3.02 (septet, *J* = 7.0 Hz, 1 H), 3.80 (s, 3 H), 6.05 (d, *J* = 9.6 Hz, 1 H), 6.72 (d, *J* = 9.5 Hz, 1 H), 6.73 (s, 1 H), 6.85 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.8 (q), 20.7 (q), 22.0 (q), 25.5 (q), 27.3 (d), 42.3 (t), 48.4 (s), 55.6 (q), 113.1 (d), 119.2 (d), 119.8 (s), 120.6 (d), 129.8 (s), 136.7 (d), 138.0 (s), 141.8 (s), 154.9 (s), 170.0 (s), 207.3 (s); exact mass *m/z* calcd for $C_{19}H_{22}O_2$ 282.1620, found 282.1616.

(3a*R,4*R**,5*S**)-4,5-Dihydroxy-1-isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one [(±)-24.2].**



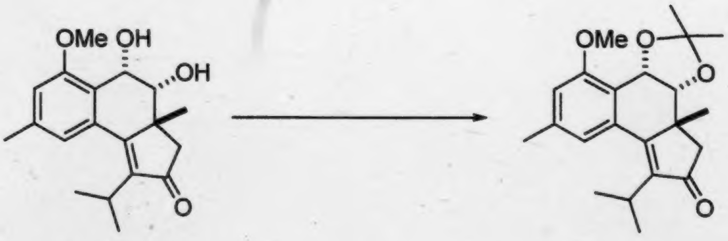
(±)-**24.1**

(±)-**24.2**

OsO_4 (50 mg, 0.20 mmol) and NMO (1.93 g, 16.00 mmol) were added to a stirred solution of olefin (±)-**24.1** (1.50 g, 5.30 mmol) in a mixture of CCl_4 (30 mL), water (6 mL), *t*-BuOH (25 mL), and acetone (40 mL) (the solvents were added in any order to the starting material) and stirring was continued for 12 h. The mixture was diluted with water (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 30 cm), using 1:4 *t*-BuOMe-CH_2Cl_2, gave diol (±)-**24.2** (1.66 g, 98%) as a colorless oil: FTIR ($CHCl_3$ cast) 3525, 2961, 1691, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 3 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.37 (d, J = 7.1 Hz, 3 H), 2.40 (s, 3 H), 2.47 (AB q, J = 18.1 Hz, $\Delta\nu_{AB}$ = 401.6 Hz, 2 H), 3.05 (s, 1 H), 3.16 (septet, J = 7.0 Hz, 1 H), 3.93 (s, 3 H), 4.04 (d, J = 4.4 Hz, 1 H), 4.36 (s, 1

H), 5.03 (d, J = 4.4 Hz, 1 H), 6.79 (s, 1 H), 6.94 (s, 1 H); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 20.0 (q), 20.5 (q), 21.9 (q), 22.1 (q), 26.1 (d), 46.1 (t), 46.4 (s), 55.6 (q), 66.5 (d), 73.1 (d), 112.7 (d), 121.4 (d), 121.6 (s), 131.5 (s), 138.8 (s), 144.6 (s), 158.6 (s), 163.9 (s), 208.1 (s); exact mass m/z calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1676.

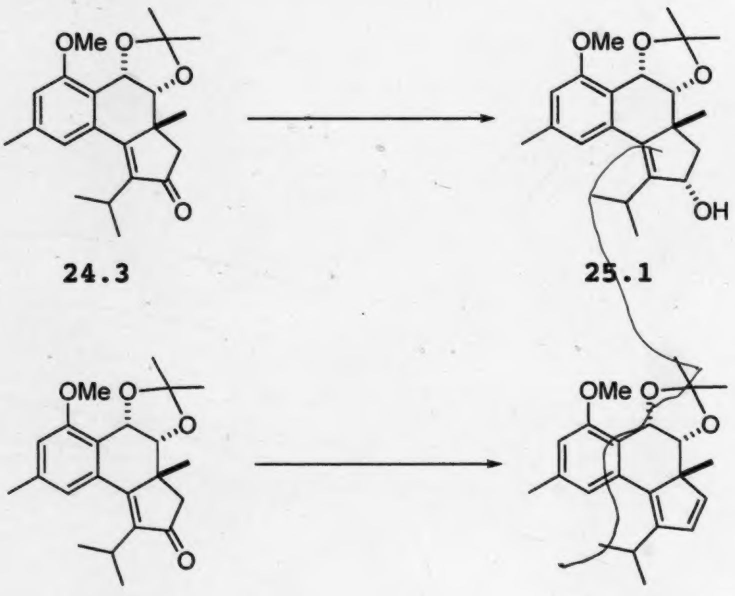
(3a*R,3b*R**,10b*S**)-6-Isopropyl-10-methoxy-2,2,3b-trimethyl-3a,3b,4,10b-tetrahydrocyclopenta[3,4]naphtho[1,2-d][1,3]dioxol-5-one (24.3).**



(±)-**24.2** **24.3**

Pyridinium *p*-toluenesulfonate (0.1 g, 0.39 mmol) was added to a stirred solution of diol (±)-**24.2** (1.30 g, 4.11 mmol) in acetone (30 mL) and 2,2-dimethoxypropane (30 mL), and the mixture was stirred at room temperature for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 X 25 mL), using 1:4 EtOAc-hexane, gave ketal **24.3** (1.29 g, 88%) as a white solid: mp 185-187 °C; FTIR (CH$_2$Cl$_2$ cast) 2961, 1697, 1607 cm^{-1}; ^{1}H NMR (C$_6$D$_6$, 400 MHz) δ 0.66 (s, 3 H), 1.14 (s, 3 H), 1.28 (s, 3 H), 1.45 (d, J = 6.9 Hz, 3 H), 1.58 (d, J = 7.0 Hz, 3 H), 2.10 (s, 3 H), 2.46 (AB q, J = 18.2 Hz, $\Delta\nu_{AB}$ = 398.6 Hz, 2 H), 3.30 (septet, J = 7.0 Hz, 1 H), 3.33 (s, 3 H), 4.04 (d, J = 6.5 Hz, 1 H), 5.56 (d, J = 6.5 Hz, 1 H), 6.42 (s, 1 H), 6.90 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 20.8 (q), 20.9 (q), 21.8 (q), 23.2 (q), 25.8 (q), 26.8 (q), 27.5 (d), 45.2 (t), 46.0 (s), 55.3 (q), 70.2 (d), 79.7 (d), 108.5 (s), 112.9 (d), 120.4 (d), 121.8 (s), 133.0 (s), 139.3 (s), 144.8 (s), 159.0 (s), 163.7 (s), 205.9 (s); exact mass *m/z* calcd for $C_{22}H_{28}O_4$ 356.1988, found 356.1983.

(3a*R,3b*R**,5*S**,10b*S**)-6-Isopropyl-10-methoxy-2,2,3b-trimethyl-3a,4,5,10b-tetrahydro-3b*H*-cyclopenta[3,4]naphtho-[1,2-d][1,3]dioxol-5-ol (25.1) and (3a*R**,3b*R**,10b*S**)-6-Isopropyl-10-methoxy-2,2,3b-trimethyl-3b,10b-dihydro-3a*H*-cyclopenta[3,4]naphtho[1,2-d][1,3]dioxole (25.2).**



24.3 **25.1**

24.3 **25.2**

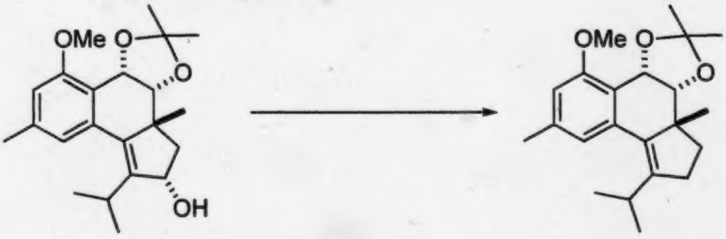
DIBAL-H (1 M, 8.0 mL, 8.00 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ketone **24.3** (1.20 g, 3.37 mmol) in CH_2Cl_2 (50 mL). After the addition, the ice-bath was removed and stirring was continued for 8 h. The mixture was cooled to 0 °C, $Na_2SO_4.10H_2O$ (2.0 g) was added, and stirring was continued for 30 min. The mixture was filtered through a Celite pad (1 x 1.5 cm), using CH_2Cl_2 (30 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25 cm), using 1:9 EtOAc-hexane, gave alcohol **25.1** (0.65 g, 54%) as a white solid and diene **25.2** (0.26 g, 23%) as white crystals.

Alcohol **25.1** had: mp 172-174 °C; FTIR (CH_2Cl_2 cast) 3500, 2959, 1608 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.74 (s, 3 H), 1.24 (s, 3 H), 1.25 (s, 3 H), 1.34 (d, J = 6.9 Hz, 3 H), 1.38 (d, J = 7.0 Hz, 3 H), 1.84 (dd, J = 7.3, 14.4 Hz, 1 H), 2.14 (s, 3 H), 2.16 (d, J = 14.4 Hz, 1 H), 3.34 (s, 3 H), 3.38 (d, J = 11.9 Hz, 1 H), 3.40 (septet, J = 7.0 Hz, 1 H), 4.07 (d, J = 6.9 Hz, 1 H), 4.95 (dd, J = 7.2, 11.9 Hz, 1 H), 5.66 (d, J = 6.9 Hz, 1 H), 6.36 (d, J = 0.6 Hz, 1 H), 6.92 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 21.8 (q), 21.9 (q), 23.9 (q), 24.4 (q), 25.0 (q), 26.8 (q), 27.4 (d), 45.0 (t), 52.6 (s), 55.2 (q), 71.5 (d), 75.9 (d), 80.3 (d), 108.3 (s), 110.7 (d), 120.2 (d), 121.0 (s), 135.8 (s), 135.9 (s), 139.0 (s), 146.9 (s), 158.9 (s); exact mass m/z calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2150.

Diene **25.2** had: mp 124-125 °C; FTIR (CH_2Cl_2 cast) 3048, 2960, 1698, 1607 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.87 (s, 3 H), 1.12 (d, J = 6.7 Hz, 3 H), 1.13 (s, 3 H), 1.26 (d, J = 6.9 Hz, 3 H), 1.38 (s, 3 H), 2.20 (s, 3 H), 3.44 (s, 3 H), 3.47 (septet, J = 7.0 Hz, 1 H), 4.53 (d, J = 6.3 Hz, 1 H), 5.72 (d, J = 6.2 Hz, 1 H), 6.42 (d, J = 5.4 Hz, 1 H), 6.44 (s, 1 H), 6.53 (d, J = 5.4 Hz, 1 H), 7.04 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 19.0 (q), 22.0 (q), 22.4 (q), 22.7 (q), 26.6 (q), 26.9 (q), 27.8 (d), 55.3 (q), 58.8

(s), 71.6 (d), 78.4 (d), 109.0 (s), 110.3 (d), 119.5 (d), 121.9 (s), 130.6 (d), 133.9 (s), 138.7 (s), 139.5 (s), 142.4 (d), 146.1 (s), 159.4 (s); exact mass *m/z* calcd for $C_{22}H_{28}O_3$ 340.2039, found 340.2039.

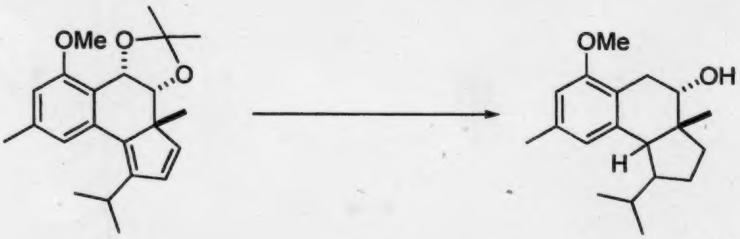
(3a*R,3b*R**,10b*S**)-6-Isopropyl-10-methoxy-2,2,3b-trimethyl-3a,4,,5,10b-tetrahydro-3b*H*-cyclopenta[3,4]-naphtho[1,2-d][1,3]dioxole (25.3).**



25.1 **25.3**

Pd-C (10%, 5 mg) was added to a solution of alcohol **25.1** (10.0 mg, 0.03 mmol) in MeOH (1 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (33 psi) for 1 h. The mixture was filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (5 mL) as a rinse, and the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using hexane, gave olefin **25.3** (7.6 mg, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2958, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (s, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 1.16 (s, 3 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 1.39 (s, 3 H), 1.50-1.58 (m, 1 H), 2.22-2.30 (m, 1 H), 2.34 (s, 3 H), 2.40-2.54 (m, 2 H), 3.32 (septet, *J* = 7.0 Hz, 1 H), 3.84 (s, 3 H), 4.25 (d, *J* = 6.4 Hz, 1 H), 5.44 (d, *J* = 6.4 Hz, 1 H), 6.59 (s, 1 H), 6.67 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 21.4 (q), 21.7 (q), 21.9 (q), 24.3 (q), 25.7 (q), 27.26 (q), 27.33 (d), 30.2 (t), 32.0 (t), 53.2 (s), 55.8 (q), 71.4 (d), 82.8 (d), 108.1 (s), 110.0 (d), 120.2 (d), 120.4 (s), 132.0 (s), 135.5 (s), 138.5 (s), 145.0 (s), 158.4 (s); exact mass *m/z* calcd for $C_{22}H_{30}O_3$ 342.2195, found 342.2203.

(3a*R,4*S**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3-3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalen-4-ol (25.4).**

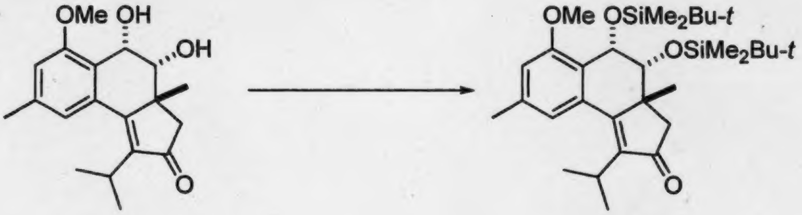


25.2 **25.4**

Pd-C (10%, 5 mg) was added to a solution of diene **25.2** (11.0 mg, 0.03 mmol) in MeOH (1 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (35 psi) for 36 h. The mixture was filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (5 mL) as a rinse, and the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:9 EtOAc-hexane, gave alcohol **25.4** (8.6 mg, 92%) as a colorless oil: FTIR (Neat) 3414, 2952, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.61 (d, J = 6.6 Hz, 3 H), 0.92-1.10 (m, 3 H), 1.08 (d, J = 6.3 Hz, 3 H), 1.24 (s, 3 H), 1.45-1.52 (m, 1 H), 1.60-1.70 (m, 1 H), 1.74-1.83 (m, 1 H), 2.20-2.28 (m, 1 H), 2.24 (s, 3 H), 2.53 (dd, J = 11.4, 15.5 Hz, 1 H), 2.98 (d, J = 6.9 Hz, 1 H), 3.22 (dd, J = 4.4, 15.6 Hz, 1 H), 3.40 (s, 3 H), 3.39-3.44 (m, 1 H), 6.37 (s, 1 H), 6.70 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 21.5 (q), 21.8 (q), 24.2 (q), 26.8 (q), 29.2 (t), 29.98 (d), 30.03 (t), 32.4 (t), 46.1 (s), 53.8

(d), 54.5 (d), 54.9 (q), 75.6 (d), 108.6 (d), 123.3 (d), 123.4 (s), 134.9 (s), 138.7 (s), 157.0 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{29}O_2$ (M + H) 289.2168, found 289.2168.

(3a*R,4*R**,5*S**)-4,5-Bis(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalen-2-one [(±)-26.1].**

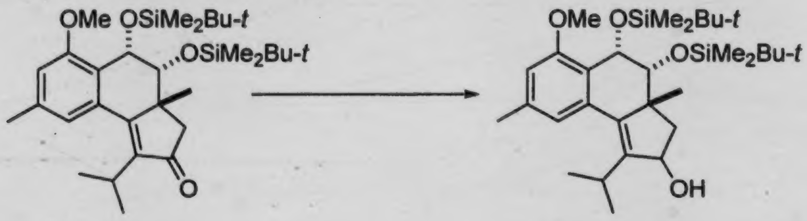


(±)-24.2 **(±)-26.1**

2,6-Lutidine (1.2 mL, 10.20 mmol), followed by *t*-$BuMe_2SiOSO_2CF_3$ (1.5 mL, 6.40 mmol), were added by rapid injection to a stirred and cooled (0 °C) solution of diol (±)-**24.2** (0.63 g, 2.00 mmol) in CH_2Cl_2 (40 mL). The ice-bath was removed and stirring was continued for 4.5 h. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:19 EtOAc-hexane, gave ketone (±)-**26.1** (0.91 g, 84%) as a colorless oil: FTIR ($CHCl_3$ cast) 2956, 1698, 1631, 1608 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ -0.24 (s, 3 H), -0.04 (s, 3 H), 0.13 (s, 3 H), 0.26 (s, 3 H), 0.89 (s, 9 H), 0.99 (s, 9 H), 1.10 (s, 3 H), 1.48 (d, *J* = 6.9 Hz, 3 H), 1.57 (d, *J* = 7.1 Hz, 3 H), 2.13 (s, 3 H), 3.15 (septet, *J* = 7.0 Hz, 1 H), 2.91 (AB q, *J* = 6.5 Hz,

$\Delta\nu_{AB}$ = 413.5 Hz, 2 H), 3.30 (s, 3 H), 3.53 (d, J = 2.7 Hz, 1 H), 5.40 (d, J = 2.7 Hz, 1 H), 6.40 (s, 1 H), 6.90 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ -5.3 (q), -4.8 (q), -4.5 (q), -3.8 (q), 18.28 (s), 18.35 (s), 20.0 (q), 21.8 (q), 21.9 (q), 25.8 (q), 26.1 (q), 26.2 (q), 32.0 (d), 44.3 (t), 50.3 (s), 55.0 (q), 67.7 (d), 77.6 (d), 111.8 (d), 120.5 (d), 124.7 (s), 134.6 (s), 139.4 (s), 140.9 (s), 156.0 (s), 169.3 (s), 206.8 (s); exact mass m/z calcd for $C_{31}H_{52}O_4Si_2$ 544.3404, found 544.340[illegible]

(2*R,3a*S**,4*S**,5*R**)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*a*]naphthalen-2-ol [(±)-26.2].**

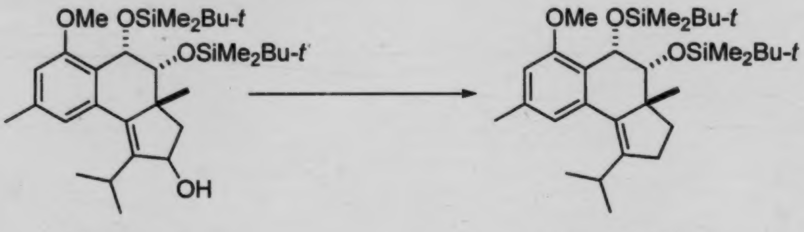


(±)-26.1 **(±)-26.2**

DIBAL-H (1 M, 4.0 mL, 4.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of enone (±)-**26.1** (0.88 g, 1.6 mmol) in CH_2Cl_2 (50 mL). After the addition, the ice-bath was removed, and stirring was continued for 10 h. The mixture was cooled to 0 °C, $Na_2SO_4.10H_2O$ (1.5 g) was added, and stirring was continued for 30 min. The mixture was filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (50 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:19 EtOAc-hexane, gave alcohol (±)-**26.2** (0.83 g, 94%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3604, 2955,

1609 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ -0.14 (s, 3 H), 0.04 (s, 3 H), 0.20 (s, 3 H), 0.34 (s, 3 H), 0.98 (s, 1 H), 1.00 (s, 3 H), 1.02 (s, 9 H), 1.07 (s, 9 H), 1.36 (d, *J* = 7.1 Hz, 3 H), 1.40 (d, *J* = 7.0 Hz, 3 H), 2.14 (s, 3 H), 2.23 (dd, *J* = 6.0, 11.7 Hz, 1 H), 2.55 (dd, *J* = 8.5, 11.7 Hz, 1 H), 3.35 (s, 3 H), 3.45 (d, *J* = 2.9 Hz, 1 H), 3.48 (septet, *J* = 7.0 Hz, 1 H), 5.10-5.18 (m, 1 H), 5.40 (d, *J* = 2.9 Hz, 1 H), 6.38 (s, 1 H), 6.95 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ -5.2 (q), -4.7 (q), -4.3 (q), -3.6 (q), 18.50 (s), 18.52 (s), 20.5 (q), 21.9 (q), 23.1 (q), 26.3 (q), 26.4 (q), 26.6 (q), 28.7 (d), 46.7 (t), 48.1 (s), 54.9 (q), 68.2 (d), 78.2 (d), 80.0 (d), 110.0 (d), 120.9 (d), 125.1 (s), 136.5 (s), 138.7 (s), 141.4 (s), 142.8 (s), 156.2 (s); exact mass *m/z* calcd for $C_{31}H_{52}O_3Si_2$ (M − H_2O) 528.3455, found 528.3440.

(3a*R,4*R**,5*S**)-4,5-Bis(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3,8a-dimethyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*a*]naphthalene [(±)-26.4].**

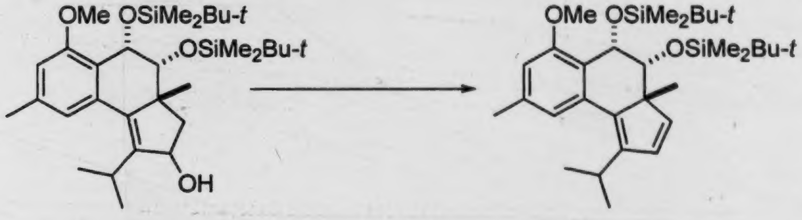


(±)-26.2 **(±)-26.4**

Pd-C (10%, 10 mg) was added to a solution of alcohol **(±)-26.2** (44 mg, 0.08 mmol) in MeOH (1:1, 1.5 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (56 psi) for 6.5 h. The mixture was then filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (10 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave crude olefin (±)-**26.4** (15 mg, ca. 35%). For characterization the compound was desilylated as follows:

Bu_4NF (1.0 M, 0.3 mL, 0.3 mmol) was added to a stirred solution of crude (±)-**26.4** (30 mg, 0.06 mmol) in THF (5 mL), and the mixture was heated at reflux for 24 h, cooled to room temperature, and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 EtOAc-hexane, gave the expected diol (16 mg, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3542, 2959, 1645, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (s, 3 H), 1.03 (d, J = 6.7 Hz, 3 H), 1.18 (d, J = 6.9 Hz, 3 H), 1.52 (septet, J = 4.3 Hz, 1 H), 2.16-2.32 (m, 1 H), 2.35 (s, 3 H), 2.48-2.56 (m, 2 H), 2.80 (d, J = 2.8 Hz, 1 H), 3.26 (septet, J = 6.8 Hz, 1 H), 3.82 (dd, J = 3.2, 4.4 Hz, 1 H), 3.88 (s, 3 H), 4.36 (d, J = 2.4 Hz, 1 H), 5.00 (dd, J = 2.0, 4.4 Hz, 1 H), 6.60 (s, 1 H), 6.90 (s, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ 21.3 (q), 21.7 (q), 21.9 (q), 22.2 (q), 27.6 (d), 29.8 (t), 31.5 (t), 53.8 (s), 55.4 (q), 67.9 (d), 74.7 (d), 109.8 (d), 120.6 (s), 120.8 (d), 130.8 (s), 133.7 (s), 138.0 (s), 146.4 (s), 158.7 (s); exact mass m/z calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1883.

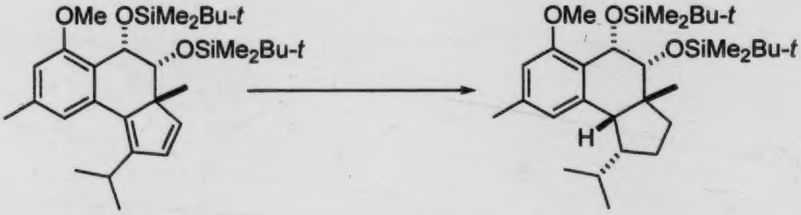
(3a*R,4*R**,5*S**)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-4,5-dihydro-3a*H*-cyclopenta[*a*]naphthalene [(±)-27.1].**



(±)-26.2 **(±)-27.1**

Et_3N (0.8 mL, 5.74 mmol) and then MsCl (0.2 mL, 2.57 mmol) were added to a stirred and cooled (0 °C) solution of alcohol (±)-**26.2** (0.50 g, 0.92 mmol) in $ClCH_2CH_2Cl$ (40 mL). The ice bath was removed, the mixture was stirred for 30 min, then heated at reflux for 4 h, and cooled to room temperature. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using hexane, gave diene (±)-**27.1** (0.39 g, 80%) as a white solid: mp 114-115 °C; FTIR ($CDCl_3$ cast) 2957, 1607 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.53 (s, 3 H), -0.02 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.66 (s, 9 H), 0.95 (s, 9 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.06 (s, 3 H), 1.16 (d, *J* = 7.0 Hz, 3 H), 2.38 (s, 3 H), 2.84 (septet, *J* = 6.8 Hz, 1 H), 3.65 (d, *J* = 2.9 Hz, 1 H), 3.80 (s, 3 H), 5.02 (d, *J* = 3.0 Hz, 1 H), 6.22 (d, *J* = 5.4 Hz, 1 H), 6.53 (d, *J* = 5.3 Hz, 1 H), 6.51 (s, 1 H), 6.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.6 (q), -4.9 (q), -4.6 (q), -3.7 (q), 18.1 (s), 18.3 (s), 21.0 (q), 21.9 (q), 24.3 (q), 25.8 (q), 25.9 (q), 26.1 (q), 28.8 (d), 55.1 (q), 57.0 (s), 67.0 (d), 77.8 (d), 109.2 (d), 119.4 (d), 125.2 (s), 126.8 (d), 136.1 (s), 138.4 (s), 143.3 (s), 144.1 (d), 145.4 (s), 155.8 (s); exact mass *m/z* calcd for $C_{31}H_{52}O_3Si_2$ 528.3455, found 528.3441.

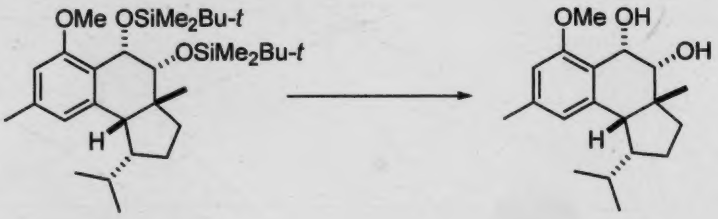
(1*R,3a*R**,4*R**,5*S**,9b*R**)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene [(±)-26.3].**



(±)-27.1 **(±)-26.3**

Pd-C (10%, 15 mg) was added to a solution of diene (±)-**27.1** (148 mg, 0.28 mmol) in MeOH-hexane (1:1, 10 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (39 psi) for 36 h. The mixture was then filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave compound (±)-**26.3** (126 mg, 85%) as a white solid: mp 93-95 °C; FTIR (CH_2Cl_2 cast) 2952, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.14 (s, 3 H), 0.00 (s, 3 H), 0.09 (s, 3 H), 0.21 (s, 3 H), 0.46 (d, *J* = 6.5 Hz, 3 H), 0.83 (s, 9 H), 0.94 (s, 9 H), 1.02 (d, *J* = 6.4 Hz, 3 H), 1.14 (s, 3 H), 1.23-1.31 (m, 1 H), 1.36-1.42 (m, 1 H), 1.58-1.76 (m, 2 H), 1.88-1.97 (m, 1 H), 2.30 (s, 3 H), 2.75 (dd, *J* = 7.3, 12.7 Hz, 1 H), 2.94 (d, *J* = 8.0 Hz, 1 H), 3.35 (d, J = 3.2 Hz, 1 H), 3.77 (s, 3 H), 4.98 (d, J = 3.1 Hz, 1 H), 6.48 (s, 1 H), 6.62 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.2 (q), -4.9 (q), -4.8 (q), -3.0 (q), 18.5 (s), 18.7 (s), 20.4 (q), 21.8 (q), 24.4 (q), 26.1 (q), 26.26 (q), 26.31 (q), 27.9 (t), 33.0 (d), 34.1 (t), 44.0 (s), 52.9 (d), 54.4 (d), 54.8 (q), 66.7 (d), 77.5 (d), 107.9 (d), 123.2 (d), 125.0 (s), 137.3 (s), 139.0 (s), 156.5 (s); exact mass *m/z* calcd for $C_{31}H_{56}O_3Si_2$ 532.3768, found 532.3770.

(1*R,3a*R**,4*R**,5*S**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-diol [(±)-27.2].**

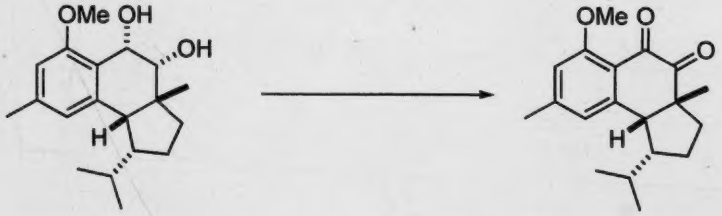


(±)-26.3 **(±)-27.2**

Bu_4NF (1.0 M, 5.0 mL, 5.0 mmol) was added to a stirred solution of compound (±)-**26.3** (0.44 g, 0.84 mmol) in THF (30 mL). The mixture was heated at reflux for 24 h, and then cooled to room temperature. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:3 EtOAc-hexane, gave diol (±)-**27.2** (0.24 g, 98%) as white crystals: mp 145-147 °C; FTIR (CH_2Cl_2 cast) 3446, 2952, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.67 (d, J = 6.6 Hz, 3 H), 1.07 (d, J

= 6.3 Hz, 3 H), 1.04-1.11 (m, 1 H), 1.16-1.24 (m, 1 H), 1.26 (s, 3 H), 1.48-1.56 (m, 2 H), 1.60-1.66 (m, 1 H), 1.85-1.93 (m, 1 H), 2.30 (s, 3 H), 2.36-2.42 (m, 1 H), 2.55 (s, 1 H), 2.97 (d, *J* = 7.0 Hz, 1 H), 3.49 (d, *J* = 4.4 Hz, 1 H), 3.83 (s, 3 H), 5.00 (d, *J* = 4.5 Hz, 1 H), 6.52 (s, 1 H), 6.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 21.5 (q), 21.9 (q), 24.0 (q), 26.5 (q), 28.0 (t), 31.1 (d), 32.8 (t), 44.2 (s), 52.6 (d), 53.6 (d), 55.4 (q), 65.6 (d), 74.7 (d), 108.3 (d), 122.9 (d), 123.2 (s), 137.7 (s), 137.9 (s), 157.9 (s); exact mass *m/z* calcd for $C_{19}H_{28}O_3$ 304.2039, found 304.2041.

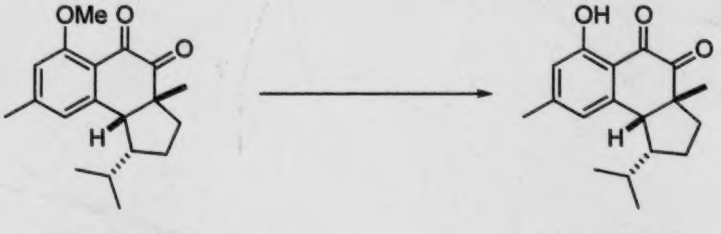
(1*R,3a*R**,9b*R**)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3-3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(±)-28.1].**



(±)-27.2 **(±)-28.1**

DMSO (0.23 mL, 3.24 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise over ca. 5 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.25 mL, 2.81 mmol) in CH_2Cl_2 (12 mL). Stirring was continued for 30 min, and diol (±)-**27.2** (200 mg, 0.66 mmol) in CH_2Cl_2 (5 mL) was added dropwise over ca. 5 min, a further portion of CH_2Cl_2 (1 mL) being used as a rinse. Stirring at -78 °C was continued for 1 h, and Et_3N (0.9 mL, 6.57 mmol) was added dropwise over ca. 2 min. Stirring was continued for 1 h, the dry-ice bath was removed and stirring was continued for 4 h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:3 EtOAc-hexane, gave diketone (±)-**28.1** (182 mg, 92%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2958, 1721, 1678, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.42 (d, J = 6.4 Hz, 3 H), 0.55 (d, J = 6.6 Hz, 3 H), 1.14-1.20 (m, 1 H), 1.25 (s, 3 H), 1.47-1.58 (m, 2 H), 1.73-1.81 (m, 1 H), 2.18-2.25 (m, 1 H), 2.38 (s, 3 H), 2.45-2.50 (m, 1 H), 3.32 (d, J = 9.5 Hz, 1 H), 3.90 (s, 3 H), 6.68 (s, 1 H), 6.75 (d, J = 0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.3 (q), 22.4 (q), 23.1 (q), 24.2 (q), 28.0 (t), 28.5 (d), 35.4 (t), 51.9 (d), 55.1 (s), 55.97 (q), 56.04 (d), 110.9 (d), 120.6 (s), 124.3 (d), 145.9 (s), 147.1 (s), 161.4 (s), 180.8 (s), 201.7 (s); exact mass m/z calcd for $C_{19}H_{24}O_3$ 300.1726, found 300.1726.

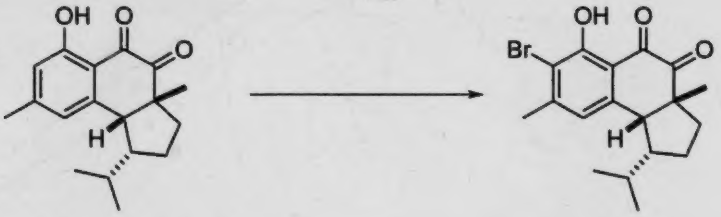
(1*R,3a*R**,9b*R**)-6-Hydroxy-1-isopropyl-3a,8-dimethyl-2,3-3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(±)-29.1].**



(±)-**28.1** (±)-**29.1**

LiCl (dried under oil pump vacuum at 100 °C for 24 h, 76 mg, 1.80 mmol) was added to a stirred solution of diketone (±)-**28.1** (180 mg, 0.60 mmol) in dry DMF (10 mL). The mixture was then heated at reflux for 20 h, cooled, diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:9 EtOAc-hexane containing 1%v/v MeOH, gave phenol (±)-**29.1** (134 mg, 78%) as yellow crystals: mp 106-108 °C; FTIR (CH_2Cl_2 cast) 2958, 1725, 1633, 1566 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.41 (d, *J* = 6.5 Hz, 3 H), 0.53 (d, *J* = 6.6 Hz, 3 H), 1.14-1.22 (m, 1 H), 1.28 (s, 3 H), 1.48-1.56 (m, 1 H), 1.62-1.71 (m, 1 H), 1.74-1.83 (m, 1 H), 2.22-2.30 (m, 1 H), 2.36 (s, 3 H), 2.61 (ddd, *J* = 5.5, 7.7, 13.1 Hz, 1 H), 3.38 (d, *J* = 9.1 Hz, 1 H), 6.67 (t, *J* = 0.7 Hz, 1 H), 6.73 (s, 1 H), 11.9 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.8 (q), 22.5 (q), 23.1 (q), 24.4 (q), 26.9 (t), 28.1 (d), 33.8 (t), 51.4 (d), 56.5 (q), 56.8 (s), 116.2 (d), 116.7 (s), 123.3 (d), 144.1 (s), 150.7 (s), 164.6 (s), 184.3 (s), 200.0 (s); exact mass *m/z* calcd for $C_{18}H_{22}O_3$ 286.1569, found 286.1567.

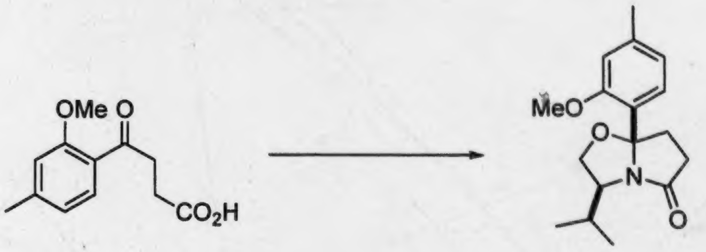
(1*R**,3a*R**,9b*R**)-7-Bromo-6-hydroxy-1-isopropyl-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(±)-Hamigeran B] [(±)-3].



(±)-**29.1** (±)-**3**

A solution of NBS (65 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) was added dropwise over ca. 10 min to a stirred and cooled (0 °C) solution of phenol (±)-**29.1** (94 mg, 0.33 mmol) and dry *i*-Pr_2NH (ca 0.03 mL, 0.21 mmol) in CH_2Cl_2 (20 mL). The cold bath was removed after the addition, and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 30 cm), using 1:19 *t*-BuOMe-hexane containing 1%v/v MeOH, gave (±)-hamigeran B [(±)-**3**] (114 mg, 94%) as a yellow solid: mp 157-159 °C; FTIR (CH_2Cl_2 cast) 2956, 1724, 1633, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.44 (d, J = 6.5 Hz, 3 H), 0.53 (d, J = 6.6 Hz, 3 H), 1.15-1.23 (m, 1 H), 1.28 (s, 3 H), 1.49-1.59 (m, 1 H), 1.63-1.72 (m, 1 H), 1.75-1.85 (m, 1 H), 2.25-2.33 (m, 1 H), 2.50 (s, 3 H), 2.62 (ddd, J = 5.5, 7.7, 13.1 Hz, 1 H), 3.38 (d, J = 9.2 Hz, 1 H), 6.82 (s, 1 H), 12.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.7 (q), 23.3 (q), 24.3 (q), 24.4 (q), 26.7 (t), 28.1 (d), 33.8 (t), 51.3 (d), 56.2 (q), 56.9 (s), 111.5 (s), 117.2 (s), 124.2 (d), 142.7 (s), 150.2 (s), 160.8 (s), 184.4 (s), 199.0 (s); exact mass *m/z* calcd for $C_{18}H_{21}{}^{79}BrO_3$ 364.0674, found 364.0679.

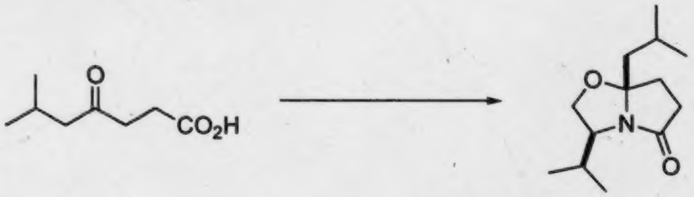
(3*S*,7a*S*)-3-Isopropyl-7a-(2-methoxy-4-methylphenyl)-tetrahydropyrrolo[2,1-b]oxazol-5(6*H*)-one (31.2).



31.1 **31.2**

(*S*)-Valinol was prepared by the literature method,[35] and had $[\alpha]_D^{25}$ = +17.4° (*c* 10, EtOH) [Lit. $[\alpha]_D^{25}$ = +17° (*c* 10, EtOH)]. Acid **31.1** (115 mg, 0.52 mmol) was added to a stirred solution of (*S*)-valinol (52.5 mg, 0.51 mmol) in PhMe (5 mL) and the solution was heated at reflux for 15 h, and then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 1:3 EtOAc-hexane, gave lactam **31.2** (126 mg, 86%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2957, 1709, 1612, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.65 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.98-1.08 (m, 1 H), 2.34 (s , 3 H), 2.32-2.38 (m, 2 H), 2.48-2.56 (m, 1 H), 2.80-2.91 (m, 1 H), 3.60-3.68 (m, 2 H), 3.82 (s, 3 H), 4.20-4.28 (m, 1 H), 6.69-6.73 (m, 2 H), 7.27 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.7 (q), 20.4 (q), 21.4 (q), 32.9 (d), 33.3 (t), 33.6 (t), 55.4 (q), 61.4 (d), 71.6 (t), 101.2 (s), 112.4 (d), 120.4 (d), 126.3 (d), 126.7 (s), 139.8 (s), 157.0 (s), 179.8 (s); exact mass *m/z* calcd for $C_{17}H_{23}NO_3$ 289.1678, found 289.1677.

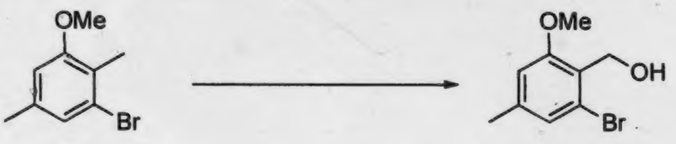
(3*S*,7a*S*)-7a-Isobutyl-3-isopropyltetrahydropyrrolo[2,1-*b*]oxazol-5-one (31.6).



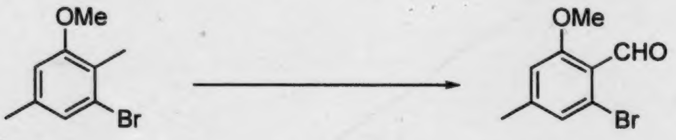
33.4 **31.6**

Acid **33.4** (4.2 g, 26.5 mmol) was added to a stirred solution of (*S*)-valinol (2.7 g, 26.5 mmol) in PhMe (150 mL) and the solution was heated at reflux for 15 h, using a Dean-Stark trap. The mixture was cooled to room temperature and then concentrated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 1:19 *t*-BuOMe-CH_2Cl_2, gave lactam **31.6** (4.5 g, 75%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2957, 2871, 1715 cm^{-1}; $[\alpha]_D = +80.5°$ (c 1.22, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.83 (d, $J = 6.7$ Hz, 3 H), 0.94 (d, $J = 6.7$ Hz, 3 H), 0.97 (d, $J = 6.7$ Hz, 3 H), 1.02 (d, $J = 6.7$ Hz, 3 H), 1.52 (dd, $J = 5.6$, 14.2 Hz, 1 H), 1.56-1.63 (m, 1 H), 1.65 (dd, $J = 7.0$, 14.3 Hz, 1 H), 1.77 (septet, $J = 6.6$ Hz, 1 H), 2.03 (td, $J = 9.9$, 13.5 Hz, 1 H), 2.23-2.30 (m, 1 H), 2.44 (ddd, $J = 2.7$, 10.4, 17.2 Hz, 1 H), 2.66 (td, $J = 9.8$, 17.2 Hz, 1 H), 3.54 (td, $J = 7.3$, 11.6 Hz, 1 H), 3.72 (dd, $J = 8.8$, 6.9 Hz, 1 H), 4.15 (dd, $J = 7.7$, 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 18.9 (q), 20.8 (q), 23.7 (q), 24.2 (q), 24.8 (d), 31.2 (t), 33.0 (t), 34.1 (d), 61.7 (d), 71.0 (t), 102.3 (s), 179.3 (s); exact mass m/z calcd for $C_{13}H_{23}O_2$ 225.1729, found 225.1721.

(2-Bromo-6-methoxy-4-methylphenyl)methanol (34.4). 2-Bromo-6-methoxy-4-methylbenzaldehyde (34.5).



34.3 **34.4**



34.3 **34.5**

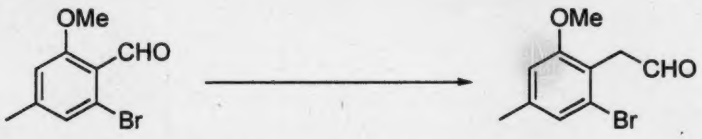
3-Bromo-2,5-dimethylanisole (**34.3**) was made by the procedure of Gore *et al.*,[37] we worked on the same scale [2,5-dimethylphenol (40.0 g, 0.33 mol), Al (4.0 g, 0.15 mol), Br_2 (100 mL, 1.87 mol), CH_2Cl_2 (200 mL)]. The resulting phenol was selectively debrominated with HI and then methylated to afford **34.3** (50.8 g, 73% over 3 steps) as a yellow oil.

NBS (19.4 g, 108 mmol) was added to a stirred and cooled (0 °C) solution of **34.3** (23.0 g, 107 mmol) in CCl_4 (350 mL). The resulting solution was irradiated (standard Pyrex apparatus) with UV light (Hanovia lamp type 30620) at 0 °C for 4 h and then filtered through a Celite pad (5 x 3 cm). After evaporation of the solvent, the residue was dissolved in dry DMSO (300 mL), $NaHCO_3$ (54.0 g, 643 mmol) was added, and the mixture was heated at 110 °C for 15 h, and cooled to room temperature. Ice water (400 mL) was added to quench the reaction, and the mixture was then extracted with Et_2O (3 x 400 mL). The combined organic extracts were washed with brine (400 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue over silica gel (5 x 40 cm), using 1:19 to 1:3 EtOAc-hexane, gave alcohol **34.4** (5.1 g, 21%) as a yellow oil and aldehyde **34.5** (10.5 g, 43%) as a yellow solid.

Alcohol **34.4** had: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.29 (s, 4 H), 3.82 (s, 3 H), 4.81 (s, 2 H), 6.63 (s, 1 H), 6.98 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 21.3 (q), 55.8 (q), 60.1 (t), 110.9 (d), 124.8 (s), 125.4 (d), 125.6 (s), 140.3 (s), 158.5 (s).

Alcohol **34.4** can be converted into aldehyde **34.5** by PCC oxidation: PCC (6.0 g, 27.3 mmol) was added to a solution of alcohol **34.4** (5.1 g, 22.2 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 8 h and filtered through a Celite pad (3 x 5 cm). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 30 cm), using 1:4 EtOAc-hexane, gave aldehyde **34.5** (4.9 g, 96%).

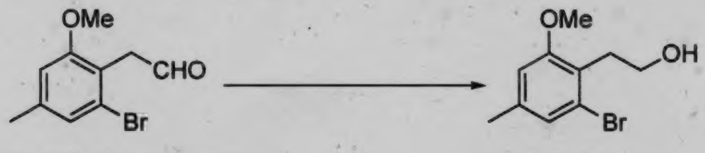
2-Bromo-6-methoxy-4-(methylphenyl)acetaldehyde (34.6).



34.5 **34.6**

$(Me_3Si)_2NK$ (0.5 M, 26.0 mL, 13.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of $Ph_3P^+CH_2(OMe)Cl^-$ (5.3 g, 15.0 mmol) in PhMe (80 mL). The ice bath was removed and stirring was continued for 1 h. Aldehyde **34.5** (2.29 g, 10.0 mmol) in PhMe (20 mL) was added dropwise, and the mixture was stirred at room temperature for 2 h. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Dilute hydrochloric acid (3 N, 50 mL) and acetone (100 mL) were added to the residue, and the mixture was heated at reflux for 3.5 h, cooled to room temperature, and then extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 1:19 EtOAc-hexane, gave aldehyde **34.6** (4.6 g, 99%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3003, 2961, 2842, 2735, 1714, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3 H), 3.78 (s, 3 H), 3.83 (d, *J* = 1.6 Hz, 2 H), 6.62 (s, 1 H), 7.03 (d, *J* = 0.7 Hz, 1 H), 9.62 (t, *J* = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.3 (q), 44.3 (t), 55.8 (q), 110.5 (d), 118.9 (s), 125.3 (d), 125.7 (s), 139.8 (s), 158.3 (s), 199.1 (s); exact mass *m/z* calcd for $C_{10}H_{11}{}^{79}BrO_2$ 241.9942, found 241.9938.

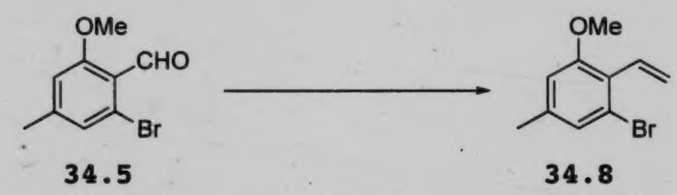
2-(2-Bromo-6-methoxy-4-methylphenyl)ethanol (34.7).



34.6 **34.7**

DIBAL-H (1.0 M, 25.0 mL, 25.0 mmol) was added dropwise over ca. 5 min to a stirred and cooled (0 °C) solution of aldehyde **34.6** (4.8 g, 19.7 mmol) in CH_2Cl_2 (100 mL). The ice bath was removed and stirring was continued for 30 min. The mixture was cooled to 0 °C, $Na_2SO_4.10H_2O$ (5 g) was added, and stirring was continued for 1 h. The mixture was filtered through a Celite pad (5 x 3 cm), using CH_2Cl_2 (100 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using 1:4 EtOAc-hexane, gave alcohol **34.7** (4.3 g, 90%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3299, 2940, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 1 H), 2.28 (s, 3 H), 3.08 (t, *J* = 6.8 Hz, 2 H), 3.76 (t, *J* = 6.8 Hz, 2 H), 3.78 (s, 3 H), 6.60 (s, 1 H), 6.99 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.1 (q), 32.9 (t), 55.8 (q), 61.9 (t), 110.6 (d), 123.8 (s), 125.4 (d), 125.5 (s), 138.5 (s), 158.2 (s); exact mass *m/z* calcd for $C_{10}H_{13}{}^{81}BrO_2$ 246.0078, found 246.0076.

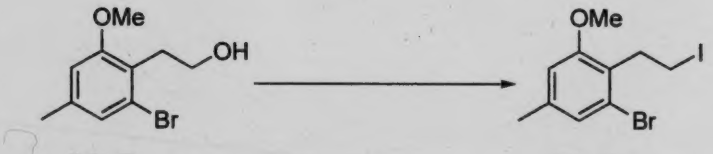
1-Bromo-3-methoxy-5-methyl-2-vinylbenzene (34.8).



$(Me_3Si)_2NK$ (0.5 M, 76.0 mL, 38.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of $Ph_3P^+CH_3Br^-$ (15.5 g, 42.5 mmol) in PhMe (40 mL). The ice bath was removed and stirring was continued for 1 h. The solution was cooled to 0 °C and a solution of aldehyde **34.5** (7.3 g, 31.9 mmol) in PhMe (20 mL) was added dropwise over ca. 5 min. The ice bath was removed and stirring was continued for 10 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 1:19 EtOAc-

hexane, gave olefin **34.8** (5.5 g, 76%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2935, 1620, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3 H), 3.81 (s, 3 H), 5.50 (dd, *J* = 2.1, 11.8 Hz, 1 H), 5.91 (dd, *J* = 2.1 Hz, 17.7 Hz, 1 H), 6.64 (s, 1 H), 6.78 (dd, *J* = 7.9, 13.8 Hz, 1 H), 7.04 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.2 (q), 55.7 (q), 111.1 (d), 120.4 (t), 123.5 (s), 124.6 (s), 125.8 (d), 131.9 (d), 138.9 (s), 158.3 (s); exact mass *m/z* calcd for $C_{10}H_{11}{}^{81}BrO$ 227.9973, found 227.9972.

1-Bromo-2-(2-iodoethyl)-3-methoxy-5-methylbenzene (34.9).

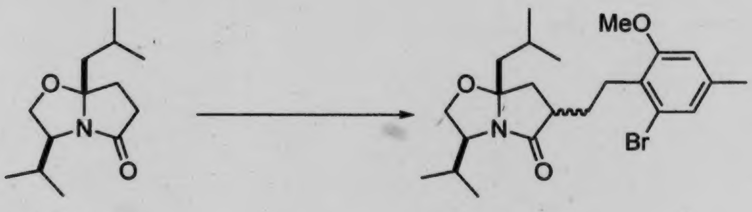


34.7 **34.9**

Et_3N (3.8 mL, 27.3 mmol), followed by MsCl (1.6 mL, 20.9 mmol) were added dropwise to a stirred and cooled (0 °C) solution of alcohol **34.7** (4.47 g, 18.2 mmol) in CH_2Cl_2 (50 mL). The cold bath was removed and stirring was continued for 2 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3 x 60 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated.

Dry NaI (11.0 g, 73.4 mmol) was added in one portion to a solution of the above residue in acetone (80 mL). The resulting mixture was heated at reflux for 24 h and cooled. The mixture was diluted with water (60 mL) and extracted with Et_2O (3 x 80 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (3.5 x 30 cm), using 1:19 EtOAc-hexane, gave **34.9** (5.9 g, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2920, 1604 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.86 (s, 3 H), 3.08 (s, 3 H), 3.14-3.18 (m, 2 H), 3.43 (t, *J* = 8.4 Hz, 2 H), 6.12 (s, 1 H), 6.85 (d, *J* = 0.6 Hz, 1 H); ^{13}C NMR (C_6D_6, 125.7 MHz) δ 1.7 (t), 21.0 (q), 34.8 (t), 55.2 (q), 110.8 (d), 125.3 (s), 125.8 (d), 126.8 (s), 139.1 (s), 158.2 (s); exact mass *m/z* calcd for $C_{10}H_{12}{}^{79}BrIO$ 353.9116, found 353.9120.

(3*S*,7a*R*)-6-[2-(2-Bromo-6-methoxy-4-methylphenyl)ethyl]-7*a*-isobutyl-3-isopropyltetrahydropyrrolo[2,1-*b*]oxazol-5-one (35.1).

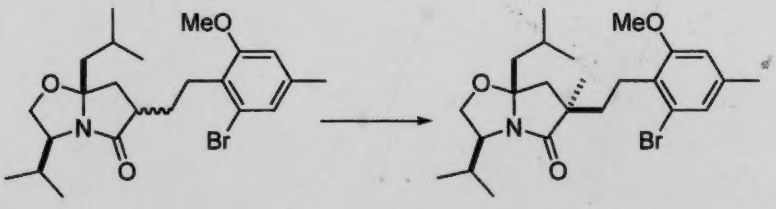


31.6 **35.1**

n-BuLi (2.5 M, 6.50 mL, 16.25 mmol) was added dropwise over ca. 5 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (2.40 mL, 17.12 mmol) in THF (80 mL). Stirring was continued for 30 min at -78 °C, and a solution of lactam **31.6** (2.43 g, 10.80 mmol) in THF (20 mL) was added dropwise over ca. 15 min. Stirring at -78 °C was continued for 1 h, and HMPA (2.20 mL, 12.64 mmol) was added dropwise, followed by iodide **34.9** (6.27 g, 17.64 mmol). The resulting mixture was stirred at -78 °C for 1 h, the cold bath was removed, and then stirring was continued for 36 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (80 mL), and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 35 cm), using 1:9 EtOAc-hexane, gave the monoalkylated lactam **35.1** as a mixture of two diastereoisomers [2.7 g, 79% yield, corrected for recovered **31.6** (730 mg, 30% recovery)].

We did not separate the isomers at this stage; however, a pure sample of the major isomer was obtained from one of the flash chromatography fractions, and it had: FTIR (CH_2Cl_2 cast) 2956, 1711, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 1.01 (d, J = 6.7 Hz, 3 H), 1.40-1.84 (m, 6 H), 2.08-2.18 (m, 1 H), 2.26 (s, 3 H), 2.60 (dd, J = 8.6, 12.8 Hz, 1 H), 2.72-2.84 (m, 3 H), 3.52-3.58 (m, 1 H), 3.72-3.80 (m, 1 H), 3.76 (s, 3 H), 4.18 (dd, J = 8.7, 9.6 Hz, 1 H), 6.56 (s, 1 H), 6.94 (t, J = 0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.0 (q), 20.8 (q), 21.1 (q), 23.9 (q), 24.2 (q), 24.9 (d), 27.3 (t), 29.9 (t), 34.2 (d), 39.6 (t), 44.2 (d), 45.0 (t), 55.6 (q), 61.1 (d), 71.0 (t), 99.9 (s), 110.4 (d), 125.06 (s), 125.09 (d), 126.9 (s), 137.9 (s), 158.0 (s), 179.7 (s); exact mass m/z calcd for $C_{23}H_{34}{}^{81}BrNO_3$ 453.1702, found 453.1696.

(3*S*,6*R*,7a*R*)-6-[2-(2-Bromo-6-methoxy-4-methylphenyl)-ethyl]-7*a*-isobutyl-3-isopropyl-6-methyltetrahydro-pyrrolo[2,1-*b*]oxazol-5-one] (35.2).

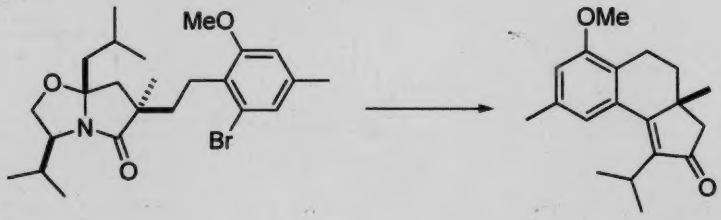


35.1 **35.2**

n-BuLi (2.5 M, 3.50 mL, 8.75 mmol) was added dropwise over ca. 5 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (1.30 mL, 9.27 mmol) in THF (40 mL), and stirring at -78 °C was continued for 30 min. A solution of lactam **35.1** (2.25 g, 5.00 mmol) in THF (10 mL) was added dropwise over ca. 15 min, and stirring at -78 °C was continued for 1.5 h. HMPA (1.20 mL, 6.90 mmol) was added dropwise over ca. 5 min, followed by MeI (1.20 mL, 19.00 mmol), which was also added over ca. 5 min. Stirring at -78 °C was continued for 1 h, the cooling bath was removed and stirring was continued for 12 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3 x 80 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 35 cm), using 1:19 *t*-BuOMe-hexane, gave the dialkylated lactam **35.2** (2.1 g, 90%) together with the *exo* isomer (0.1 g, 5%). Lactam **35.2** had: FTIR (CH_2Cl_2 cast) 2956, 1711, 1604 cm^{-1}; $[\alpha]_D$ = +18.6° (*c* 0.500, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 1.24 (s, 3

H), 1.51-1.90 (m, 6 H), 2.20 (AB q, J = 13.9 Hz, $\Delta\nu_{AB}$ = 223.6 Hz, 2 H), 2.23 (s, 3 H), 2.70-2.83 (m, 2 H), 3.53-3.67 (m, 2 H), 3.76 (s, 3 H), 4.18 (t, J = 7.9 Hz, 1 H), 6.56 (s, 1 H), 6.95 (t, J = 0.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.0 (q), 20.9 (q), 21.1 (q), 23.4 (q), 23.6 (q), 24.2 (q), 24.9 (d), 25.0 (t), 34.5 (d), 38.1 (t), 43.6 (t), 45.2 (t), 47.4 (s), 55.7 (q), 62.1 (d), 70.3 (t), 99.1 (s), 110.4 (d), 124.8 (s), 125.0 (d), 126.9 (s), 137.9 (s), 157.8 (s), 184.3 (s); exact mass m/z calcd for $C_{24}H_{36}{}^{81}BrNO_3$ 467.1858, found 467.1861.

(3a*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one [(-)-21.4].

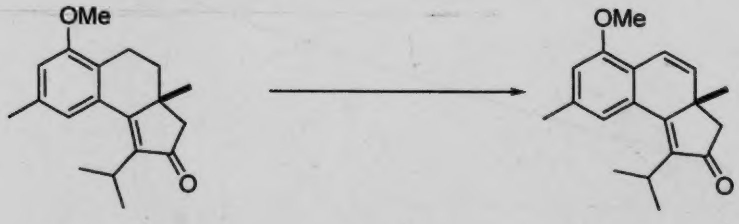


35.2 **(-)-21.4**

t-BuLi (1.7 M, 7.0 mL, 11.9 mmol) was added dropwise over ca. 15 min to a stirred and cooled (-78 °C) solution of lactam **35.2** (2.1 g, 4.5 mmol) in THF (30 mL). Stirring at -78 °C was continued for 1.75 h, and the mixture was then quenched by addition of aqueous n-$Bu_4NH_2PO_4$ (1.0 M, 50 mL, 50 mmol). The organic solvent (THF) was concentrated at room temperature [rotary evaporator] and the aqueous residue was heated at reflux for 24 h. The mixture was cooled to room temperature and extracted with Et_2O (3 x 80 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated.

Aqueous NaOH (5 N, 15 mL) was added to a solution of the above residue in EtOH (20 mL). This mixture was heated at reflux (oil bath at 100 °C) for 24 h, cooled to room temperature and then extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:9 EtOAc-hexane, gave enone (-)-**21.4** (1.15 g, 90%) as a yellow oil: FTIR ($CHCl_3$ cast) 2957, 1693, 1610 cm^{-1}; $[\alpha]_D = -345.1°$ (*c* 0.304, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 3 H), 1.19 (d, *J* = 6.9 Hz, 3 H), 1.37 (d, *J* = 7.0 Hz, 3 H), 1.66-1.74 (m, 1 H), 2.07 (ddd, *J* = 1.0, 6.9, 13.2 Hz, 1 H), 2.26 (AB q, *J* = 18.5 Hz, $\Delta\nu_{AB}$ = 48.9 Hz, 2 H), 2.37 (s, 3 H), 2.61-2.71 (m, 1 H), 2.86 (dd, *J* = 7.0, 18.8 Hz, 1 H), 3.12 (septet, *J* = 7.0 Hz, 1 H), 3.83 (s, 3 H), 6.70 (s, 1 H), 6.86 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.8 (q), 20.6 (q), 20.8 (t), 21.7 (q), 23.0 (q), 25.7 (d), 36.0 (t), 38.7 (t), 51.1 (s), 55.3 (q), 111.8 (d), 120.9 (d), 123.5 (s), 131.5 (s), 136.0 (s), 140.6 (s), 157.2 (s), 170.1 (s), 208.2 (s); exact mass *m/z* calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1774.

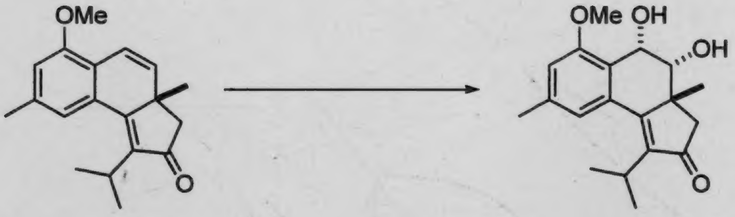
(3a*S*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-3,3a-dihydrocyclopenta[*a*]naphthalen-2-one [(-)-24.1].



(-)-21.4 **(-)-24.1**

DDQ (1.36 g, 6.0 mmol) was added in one portion to a stirred solution of enone (-)-**21.4** (1.15 g, 4.0 mmol) in 1,4-dioxane (60 mL) and the mixture was heated at reflux for 10 h (Ar atmosphere). The mixture was cooled to room temperature and filtered through a pad of silica gel (5 x 3.5 cm), using Et_2O (100 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 30 cm), using 1:9 EtOAc-hexane, gave ketone (-)-**24.1** (0.83 g, 74%) as a yellow oil: FTIR ($CHCl_3$ cast) 2958, 1696, 1603 cm^{-1}; $[\alpha]_D = -786.9°$ (*c* 0.352, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, J = 6.8 Hz, 3 H), 1.18 (s, 3 H), 1.36 (d, J = 7.1 Hz, 3 H), 2.40 (s, 3 H), 2.44 (AB q, J = 17.6 Hz, $\Delta\nu_{AB}$ = 108.8 Hz, 2 H), 3.02 (septet, J = 7.0 Hz, 1 H), 3.80 (s, 3 H), 6.05 (d, J = 9.6 Hz, 1 H), 6.72 (d, J = 9.5 Hz, 1 H), 6.73 (s, 1 H), 6.85 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.8 (q), 20.7 (q), 22.0 (q), 25.5 (q), 27.3 (d), 42.3 (t), 48.4 (s), 55.6 (q), 113.1 (d), 119.2 (d), 119.8 (s), 120.6 (d), 129.8 (s), 136.7 (d), 138.0 (s), 141.8 (s), 154.9 (s), 170.0 (s), 207.3 (s); exact mass *m/z* calcd for $C_{19}H_{22}O_2$ 282.1620, found 282.1615.

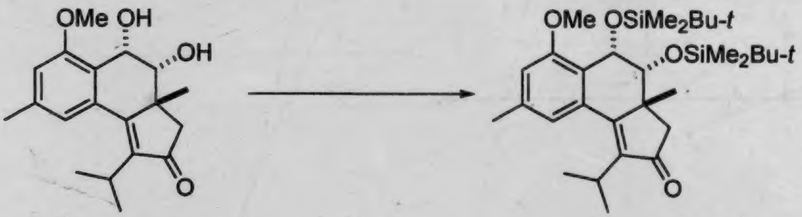
(3a*R*,4*R*,5*S*)-4,5-Dihydroxy-1-isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one [(-)-24.2].



(-)-24.1 **(-)-24.2**

OsO_4 (50 mg, 0.2 mmol) and NMO (0.83 g, 6.9 mmol) were added to a stirred solution of olefin (-)-**24.1** (0.65 g, 2.3 mmol) in a mixture of CCl_4 (20 mL), water (5 mL), *t*-BuOH (20 mL), and acetone (30 mL) (the solvents were added in any order to the starting material), and stirring was continued for 12 h. Water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:4 *t*-BuOMe-CH_2Cl_2, gave diol (-)-**24.2** [0.45 g, 81% corrected for recovered (-)-**24.1** (0.15 g, 23%)] as a colorless oil: FTIR ($CHCl_3$ cast) 3525, 2961, 1691, 1608 cm^{-1}; $[\alpha]_D = -245.4°$ (*c* 0.324, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 3 H), 1.23 (d, $J = 6.8$ Hz, 3 H), 1.37 (d, $J = 7.1$ Hz, 3 H), 2.40 (s, 3 H), 2.47 (AB q, $J = 18.1$ Hz, $\Delta\nu_{AB} = 321.9$ Hz, 2 H), 3.05 (s, 1 H), 3.16 (septet, $J = 7.0$ Hz, 1 H), 3.93 (s, 3 H), 4.04 (d, $J = 4.4$ Hz, 1 H), 4.36 (s, 1 H), 5.03 (d, $J = 4.4$ Hz, 1 H), 6.79 (s, 1 H), 6.94 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.0 (q), 20.5 (q), 21.9 (q), 22.1 (q), 26.1 (d), 46.1 (t), 46.4 (s), 55.6 (q), 66.5 (d), 73.1 (d), 112.7 (d), 121.4 (d), 121.6 (s), 131.5 (s), 138.8 (s), 144.6 (s), 158.6 (s), 163.9 (s), 208.1 (s); exact mass *m/z* calcd for $C_{19}H_{24}O_4$ 316.1674, found 316.1670.

(3a*R*,4*R*,5*S*)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene-2-one [(-)-26.1].

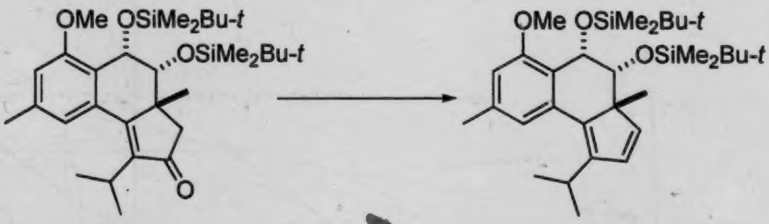


(-)-24.2 **(-)-26.1**

2,6-Lutidine (1.0 mL, 8.50 mmol), followed by t-$BuMe_2SiOSO_2CF_3$ (1.3 mL, 5.55 mmol), was added by rapid injection to a stirred and cooled (0 °C) solution of diol (-)-**24.2** (0.43 g, 1.36 mmol) in CH_2Cl_2 (40 mL). The ice-bath was removed and stirring was continued for 4.5 h. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:19 EtOAc-hexane, gave ketone (-)-**26.1** (0.54 g, 73%) as a colorless oil: FTIR ($CHCl_3$ cast) 2956, 1698, 1631, 1608 cm^{-1}; $[\alpha]_D = -169.7°$ (*c* 0.254, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ -0.48 (s, 3 H), -0.03 (s, 6 H), 0.10 (s, 3 H), 0.70 (s, 9 H), 0.92 (s, 9 H), 1.08 (s, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 1.28 (d, *J* = 7.1 Hz, 3 H), 2.40 (s, 3 H), 2.61 (AB q, *J* = 16.8 Hz, $\Delta\nu_{AB}$ = 392.6 Hz, 2 H), 2.84 (septet, *J* = 7.0 Hz, 1 H), 3.43 (d, *J*

= 2.7 Hz, 1 H), 3.82 (s, 3 H), 5.12 (d, J = 2.6 Hz, 1 H), 6.68 (s, 1 H), 6.75 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.7 (q), -5.0 (q), -4.9 (q), -3.9 (q), 17.9 (s), 18.1 (s), 19.5 (q), 21.4 (q), 21.9 (q), 24.8 (q), 25.81 (q), 25.83 (q), 31.8 (d), 44.2 (t), 50.1 (s), 55.3 (q), 67.0 (d), 76.9 (d), 111.7 (d), 120.0 (d), 124.2 (s), 133.7 (s), 139.1 (s), 140.1 (s), 155.5 (s), 171.1 (s), 209.2 (s); exact mass *m/z* calcd for $C_{31}H_{52}O_4Si_2$ 544.3404, found 544.3400.

(3a*R*,4*R*,5*S*)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-4,5-dihydro-3a*H*-cyclopenta[*a*]naphthalene [(+)-27.1].



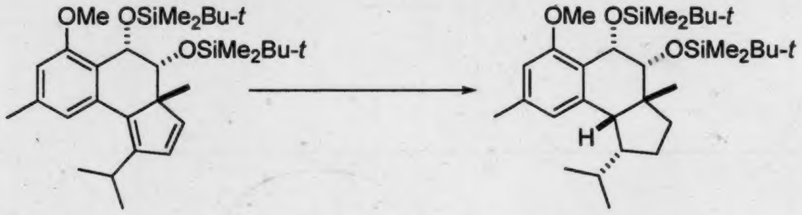
(-)-26.1 **(+)-27.1**

DIBAL-H (1.0 M, 2.0 mL, 2.00 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ketone **(-)-26.1** (0.47 g, 0.87 mmol) in CH_2Cl_2 (15 mL). After the addition, the ice-bath was removed and stirring was continued for 10 h. The mixture was cooled to 0 °C, $Na_2SO_4.10H_2O$ (0.5 g) was added slowly, and stirring was continued for 30 min. The resulting mixture was filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (20 mL) as a rinse. The solvent was concentrated and the residue [crude (-)-**26.2**] was dissolved in $ClCH_2CH_2Cl$ (40 mL).

Et_3N (0.8 mL, 5.74 mmol), followed by MsCl (0.2 mL, 2.57 mmol), were added to the above stirred solution.

Stirring was continued for 30 min at room temperature, for 4 h at reflux (oil bath at 85 °C), and the mixture was cooled to room temperature. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using hexane, gave diene (+)-**27.1** (0.39 g, 84%) as a colorless oil: FTIR ($CHCl_3$ cast) 2958, 1607 cm^{-1}; $[\alpha]_D = +2.76°$ (*c* 0.290, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ -0.53 (s, 3 H), -0.02 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.66 (s, 9 H), 0.95 (s, 9 H), 0.98 (d, J = 6.8 Hz, 3 H), 1.06 (s, 3 H), 1.16 (d, J = 7.0 Hz, 3 H), 2.38 (s, 3 H), 2.84 (septet, J = 6.8 Hz, 1 H), 3.65 (d, J = 2.9 Hz, 1 H), 3.80 (s, 3 H), 5.02 (d, J = 3.0 Hz, 1 H), 6.22 (d, J = 5.4 Hz, 1 H), 6.53 (d, J = 5.3 Hz, 1 H), 6.51 (s, 1 H), 6.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.6 (q), -4.9 (q), -4.6 (q), -3.7 (q), 18.1 (s), 18.3 (s), 21.0 (q), 21.9 (q), 24.3 (q), 25.8 (q), 25.9 (q), 26.1 (q), 28.8 (d), 55.1 (q), 57.0 (s), 67.0 (d), 77.8 (d), 109.2 (d), 119.4 (d), 125.2 (s), 126.8 (d), 136.1 (s), 138.4 (s), 143.3 (s), 144.1 (d), 145.4 (s), 155.8 (s); exact mass *m/z* calcd for $C_{31}H_{52}O_3Si_2$ 528.3455, found 528.3445.

(1*R*,3a*R*,4*R*,5*S*,9b*R*)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-isopropyl-6-methoxy-3a,8-dimethyl-2,3-3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene [(+)-26.3].

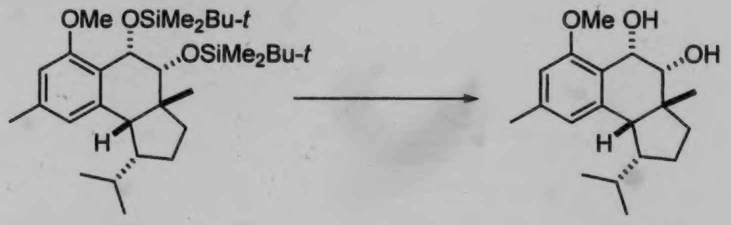


(+)-**27.1** (+)-**26.3**

Pd-C (10%, 20 mg) was added to a solution of diene (+)-**27.1** (300 mg, 0.57 mmol) in MeOH-hexane (1:1, 20 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (39 psi) for 40 h. The mixture was then filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (50 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using hexane, gave compound (+)-**26.3** [217 mg, 78%, corrected for recovered (+)-**27.1** (24 mg, 8%] as a colorless oil: FTIR (CH_2Cl_2 cast) 2952, 1612 cm^{-1}; $[\alpha]_D$ = +37.7° (*c* 0.170, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ -0.14 (s, 3 H), 0.00 (s, 3 H), 0.09 (s, 3 H), 0.21 (s, 3 H), 0.46 (d, *J* = 6.5 Hz, 3 H), 0.83 (s, 9 H), 0.94 (s, 9 H), 1.02 (d, *J* = 6.4 Hz, 3 H), 1.14 (s, 3 H), 1.23-1.31 (m, 1 H), 1.36-1.42 (m, 1 H), 1.58-1.76 (m, 2 H), 1.88-1.97 (m, 1 H), 2.30 (s, 3 H), 2.75 (dd, *J* = 7.3, 12.7 Hz, 1 H), 2.94 (d, *J* = 8.0 Hz, 1 H), 3.35 (d, *J* = 3.2 Hz, 1 H), 3.77 (s, 3 H), 4.98 (d, *J* = 3.1 Hz, 1 H), 6.48 (s, 1 H), 6.62 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.2 (q), -4.9 (q), -4.8 (q), -3.0 (q), 18.5 (s), 18.7 (s), 20.4 (q), 21.8 (q), 24.4 (q), 26.1 (q), 26.26 (q), 26.31 (q), 27.9

(t), 33.0 (d), 34.1 (t), 44.0 (s), 52.9 (d), 54.4 (d), 54.8 (q), 66.7 (d), 77.5 (d), 107.9 (d), 123.2 (d), 125.0 (s), 137.3 (s), 139.0 (s), 156.5 (s); exact mass *m/z* calcd for $C_{27}H_{47}O_3Si_2$ (M − C_4H_9) 475.3064, found 475.3063.

(1*R*,3a*R*,4*R*,5*S*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3-3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]-naphthalene-4,5-diol [(+)-27.2].

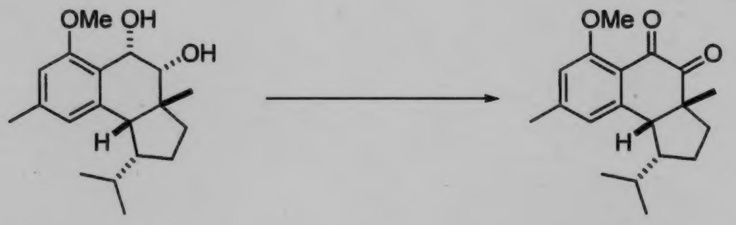


(+)-26.3 **(+)-27.2**

Bu_4NF (1.0 M, 3.0 mL, 3.0 mmol) was added to a stirred solution of compound (+)-**26.3** (0.20 g, 0.37 mmol) in THF (20 mL). The mixture was heated at reflux for 19 h, and then cooled to room temperature. Saturated aqueous NH_4Cl (15 mL) was added and the mixture was then extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:3 EtOAc-hexane, gave diol (+)-**27.2** (98 mg, 85%) as white crystals: mp 145-147 °C; FTIR (CH_2Cl_2 cast) 3446, 2952, 1610 cm^{-1}; $[\alpha]_D = +82.0°$ (*c* 0.161, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.67 (d, *J* = 6.6 Hz, 3 H), 1.07 (d, *J* = 6.3 Hz, 3 H), 1.04-1.11 (m, 1 H), 1.16-1.24 (m, 1 H), 1.26 (s, 3 H), 1.48-1.56 (m, 2 H), 1.60-1.66 (m, 1 H), 1.85-1.93 (m, 1 H), 2.30 (s, 3 H), 2.36-2.42 (m, 1 H), 2.55 (s, 1 H), 2.97 (d, *J* = 7.0 Hz, 1 H), 3.49 (d, *J* = 4.4 Hz, 1 H), 3.83

(s, 3 H), 5.00 (d, J = 4.5 Hz, 1 H), 6.52 (s, 1 H), 6.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 21.5 (q), 21.9 (q), 24.0 (q), 26.5 (q), 28.0 (t), 31.1 (d), 32.8 (t), 44.2 (s), 52.6 (d), 53.6 (d), 55.4 (q), 65.6 (d), 74.7 (d), 108.3 (d), 122.9 (d), 123.2 (s), 137.7 (s), 137.9 (s), 157.9 (s); exact mass *m/z* calcd for $C_{19}H_{28}O_3$ 304.2039, found 304.2032.

(1*R*,3a*R*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(-)-28.1].

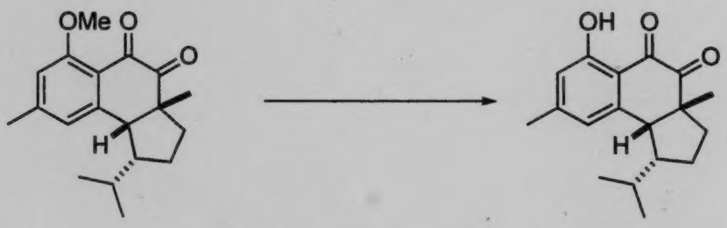


(+)-27.2 **(-)-28.1**

DMSO (0.15 mL, 2.11 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise over ca. 5 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.15 mL, 1.68 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 30 min, and diol (+)-**27.2** (81 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) was added dropwise over ca. 5 min. Stirring at -78 °C was continued for 1 h, and Et_3N (0.7 mL, 5.00 mmol) was added dropwise over ca. 2 min. Stirring was continued for 1 h, the dry-ice bath was removed, and stirring was continued for 4 h. Saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:3 EtOAc-hexane, gave

diketone (-)-**28.1** (75 mg, 94%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2958, 1721, 1678, 1605 cm^{-1}; $[\alpha]_D$ = -187.1° (*c* 0.124, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.42 (d, *J* = 6.4 Hz, 3 H), 0.55 (d, *J* = 6.6 Hz, 3 H), 1.14-1.20 (m, 1 H), 1.25 (s, 3 H), 1.47-1.58 (m, 2 H), 1.73-1.81 (m, 1 H), 2.18-2.25 (m, 1 H), 2.38 (s, 3 H), 2.45-2.50 (m, 1 H), 3.32 (d, *J* = 9.5 Hz, 1 H), 3.90 (s, 3 H), 6.68 (s, 1 H), 6.75 (d, *J* = 0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.3 (q), 22.4 (q), 23.1 (q), 24.2 (q), 28.0 (t), 28.5 (d), 35.4 (t), 51.9 (d), 55.1 (s), 55.97 (q), 56.04 (d), 110.9 (d), 120.6 (s), 124.3 (d), 145.9 (s), 147.1 (s), 161.4 (s), 180.8 (s), 201.7 (s); exact mass *m/z* calcd for $C_{19}H_{24}O_3$ 300.1726, found 300.1722.

(1*R*,3a*R*,9b*R*)-6-Hydroxy-1-isopropyl-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(-)-29.1].

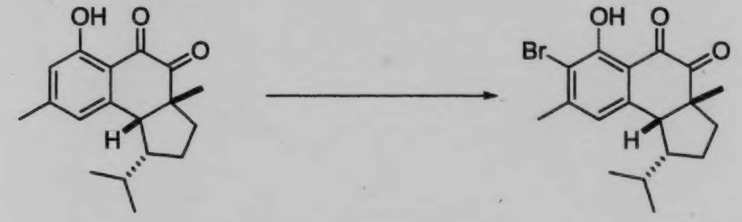


(-)-**28.1** (-)-**29.1**

LiCl (dried under oil pump vacuum at 100 °C for 24 h, 29 mg, 0.68 mmol) was added to a stirred solution of diketone (-)-**28.1** (45 mg, 0.15 mmol) in DMF (10 mL). The mixture was heated at reflux for 20 h, cooled, diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the

residue over silica gel (1 x 20 cm), using 1:9 EtOAc-hexane containing 1%v/v MeOH, gave phenol (-)-**29.1** (37 mg, 87%) as yellow crystals: mp 108-109 °C; FTIR (CH_2Cl_2 cast) 2958, 1725, 1633, 1566 cm^{-1}; $[\alpha]_D = -203.1°$ (*c* 0.128, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.41 (d, *J* = 6.5 Hz, 3 H), 0.53 (d, *J* = 6.6 Hz, 3 H), 1.14-1.22 (m, 1 H), 1.28 (s, 3 H), 1.48-1.56 (m, 1 H), 1.62-1.71 (m, 1 H), 1.74-1.83 (m, 1 H), 2.22-2.30 (m, 1 H), 2.36 (s, 3 H), 2.61 (ddd, *J* = 5.5, 7.7, 13.1 Hz, 1 H), 3.38 (d, *J* = 9.1 Hz, 1 H), 6.67 (t, *J* = 0.7 Hz, 1 H), 6.73 (s, 1 H), 11.9 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.8 (q), 22.5 (q), 23.1 (q), 24.4 (q), 26.9 (t), 28.1 (d), 33.8 (t), 51.4 (d), 56.5 (q), 56.8 (s), 116.2 (d), 116.7 (s), 123.3 (d), 144.1 (s), 150.7 (s), 164.6 (s), 184.3 (s), 200.0 (s); exact mass *m/z* calcd for $C_{18}H_{22}O_3$ 286.1569, found 286.1567.

(1*R*,3a*R*,9b*R*)-7-Bromo-6-hydroxy-1-isopropyl-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-4,5-dione [(-)-Hamigeran B] [(-)-3].



(-)-**29.1** (-)-**3**

A solution of NBS (2.5 mg, 0.015 mmol) in CH_2Cl_2 (1 mL) was added dropwise over ca. 10 min to a stirred and cooled (0 °C) solution of phenol (-)-**29.1** (4 mg, 0.014 mmol) and dry *i*-Pr_2NH (ca 0.01 mL, 0.07 mmol) in CH_2Cl_2 (2 mL). The cold bath was removed after the addition, and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 1:19 *t*-BuOMe-hexane, containing 1%v/v MeOH, gave (-)-hamigeran B [(-)-**3**] (4.5 mg, 88%) as a yellow solid: mp 165-167 °C; FTIR (CH_2Cl_2 cast) 2956, 1724, 1633, 1609 cm^{-1}; $[\alpha]_D = -176.4°$ (*c* 0.142, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.44 (d, *J* = 6.5 Hz, 3 H), 0.53 (d, *J* = 6.6 Hz, 3 H), 1.15-1.23 (m, 1 H), 1.28 (s, 3 H), 1.49-1.59 (m, 1 H), 1.63-1.72 (m, 1 H), 1.75-1.85 (m, 1 H), 2.25-2.33 (m, 1 H), 2.50 (s, 3 H), 2.62 (ddd, *J* = 5.5, 7.7, 13.1 Hz, 1 H), 3.38 (d, *J* = 9.2 Hz, 1 H), 6.82 (s, 1 H), 12.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.7 (q), 23.3 (q), 24.3 (q), 24.4 (q), 26.7 (t), 28.1 (d), 33.8 (t), 51.3 (d), 56.2 (q), 56.9 (s), 111.5 (s), 117.2 (s), 124.2 (d), 142.7 (s), 150.2 (s), 160.8 (s), 184.4 (s), 199.0 (s); exact mass *m/z* calcd for $C_{18}H_{21}{}^{79}BrO_3$ 364.0674, found 364.0679.

IV References and Notes

1 Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1-6.

2 Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79-85.

3 Cambie, R. C.; Rickard, C. E. F.; Rutledge, P. S.; Wellington, K. D. *Acta Crystallogr.* **2001**, *C57*, 958-960.

4 Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 3675-3678.

5 Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 3679-3683.

6 Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613-627.

7 Clive, D. L. J.; Wang, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 3406-3409.

8 Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049-7053.

9 Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480-4481.

10 Lange, G. L.; Neidert, E. E.; Orrom, W. J.; Wallace, D. J. *Can. J. Chem.* **1978**, *56*, 1628-1633.

11 Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765-5775.

12 Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759-6760.

13 (a) Nishimura, S.; Mochizuki, F.; Kobayakawa, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1919. (b) Nishimura, S.; Sakamoto, H.; Ozawa, T. *Chem. Lett.* **1973**, 855. (c) Siegel, S.; Smith, G. V. *J. Am. Chem. Soc.* **1960**, *82*, 6082-6087.

14 Cooke, R. G.; Dowd, H. *Aust. J. Chem.* **1953**, *6*, 53-57.

15 Martin, E. L. *J. Am. Chem. Soc.* **1936**, *58*, 1438-1442.

16 Cf. Ruzicka, L.; Hösli, H.; Hofmann, K. *Helv. Chim. Acta* **1936**, *19*, 370-377.

17 Cf. Snowden, R. G.; Sonnay, P.; Ohloff, G. *Helv. Chim. Acta* **1981**, *64*, 25-32.

18 Cf. Yatabe, T.; Kayakiri, H.; Kawai, Y.; Oku, T.; Tanaka, H. *Chem. Pharm. Bull.* **1998**, *46*, 1556-1565.

19 Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37-38.

20 Cf. Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588-1589.

21 Cf. Johnson, W. S.; Kemp, A. D.; Pappo, R.; Ackerman, J.; Johns, W. F. *J. Am. Chem. Soc.* **1956**, *78*, 6312-6321.

22 Macro, M.; Hammock, B. D.; Kurth, M. J. *J. Org. Chem.* **1993**, *58*, 7548-7556.

23 Cf. Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592-4597.

24 Cf. Hauser, F. M.; Prasanna, S. *Synthesis* **1980**, 621-623.

25 Owton, W. M.; Brunavs, M.; Miles, M. V.; Dobson, D. R.; Steggles, D. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 931-934.

26 (a) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576-1579. (b) Krohn, K.; Bernard, S.; Flörke, U.; Hayat, N. *J. Org. Chem.* **2000**, *65*, 3218-3222.

27 Cf. Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, *56*, 631-637.

28 For studies on the mechanism of hydrogenolysis, see: Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *64*, 4172-4173.

29 Colvin, E. *Silicon in Organic Synthesis*, Butterworth's, London, **1981**, p 12.

30 Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivoldini, A. *Synthesis* **1987**, 287-288.

31 Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936-1938.

32 Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 7507-7515.

33 Solladie, G.; Almario, A. *Tetrahedron Asym.* **1995**, *6*, 559-576.

34 Cf. McGhie, J. F.; Ross, W. A.; Evans, D.; Tomlin, J. E. *J. Chem. Soc.* **1962**, 350-355.

35 McKennon, M.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568-3571.

36 Burgess, L.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656-1662.

37 Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1992**, *57*, 2774-2783.

38 Britlain, J. M.; de la Mare, P. B. D.; Newman, P. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 32-41.

39 Leed, A.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098-1106.

40 (a) Helms, A.; Heiler, D.; McLendon, G. *J. Am. Chem. Soc.* **1992**, *114*, 6227-6238. (b) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247-260. (c) Mizutani, T.; Wada, K.; Kitagawa, S. *J. Org. Chem.* **2000**, *65*, 6097-6106.

V, NMR Spectra

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Sample JW-07-187
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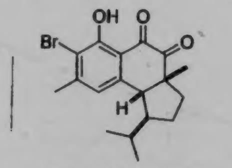
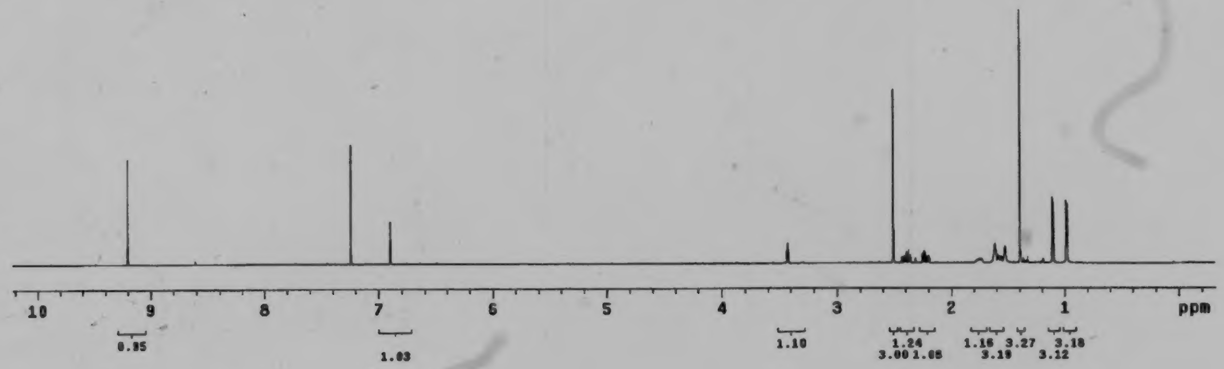
acq.time[s]:2.0   relax. time[s]:3.0   dig.res.[Hz/pt]:0.11   # of scans: 82

Pulse Sequence: s2pul

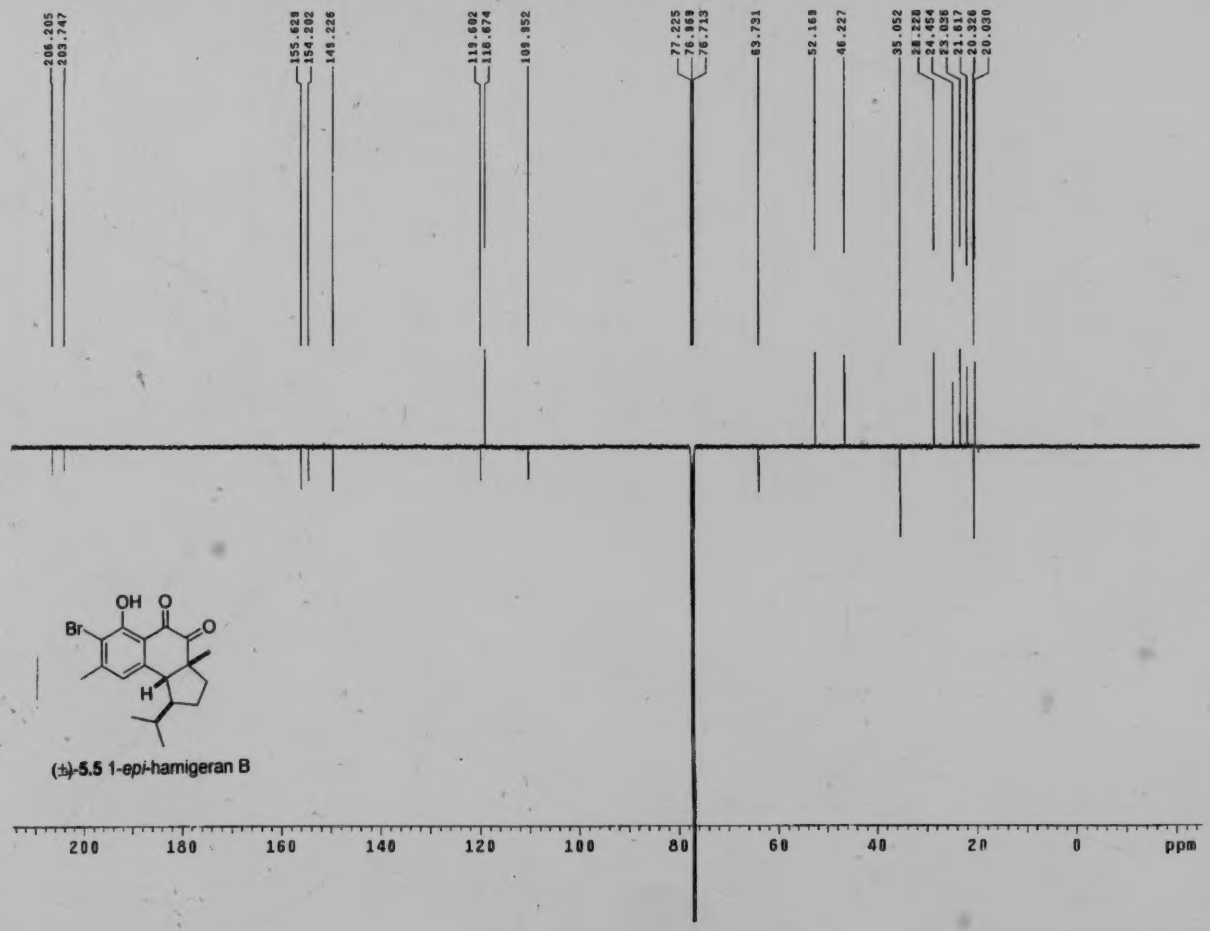


(±)-**5.5** 1-*epi*-hamigeran B



125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
CH, CH3 positive; C, CH2 negative Sample JW-07-185
date:Aug 14 2002 seqfil:apt hz/mm:125.08 sweep width[Hz]:30019 spectrometer:i300 file:/mnt/d600/clivenmrdata/Jian/notebook07/jw07185-1-13c.fid
acq.time[s]:2.0 relax. time[s]:0.5 dig.res.[Hz/pt]:0.46 # of scans:13464

Pulse Sequence: apt



(±)-**5.5** 1-*epi*-hamigeran B

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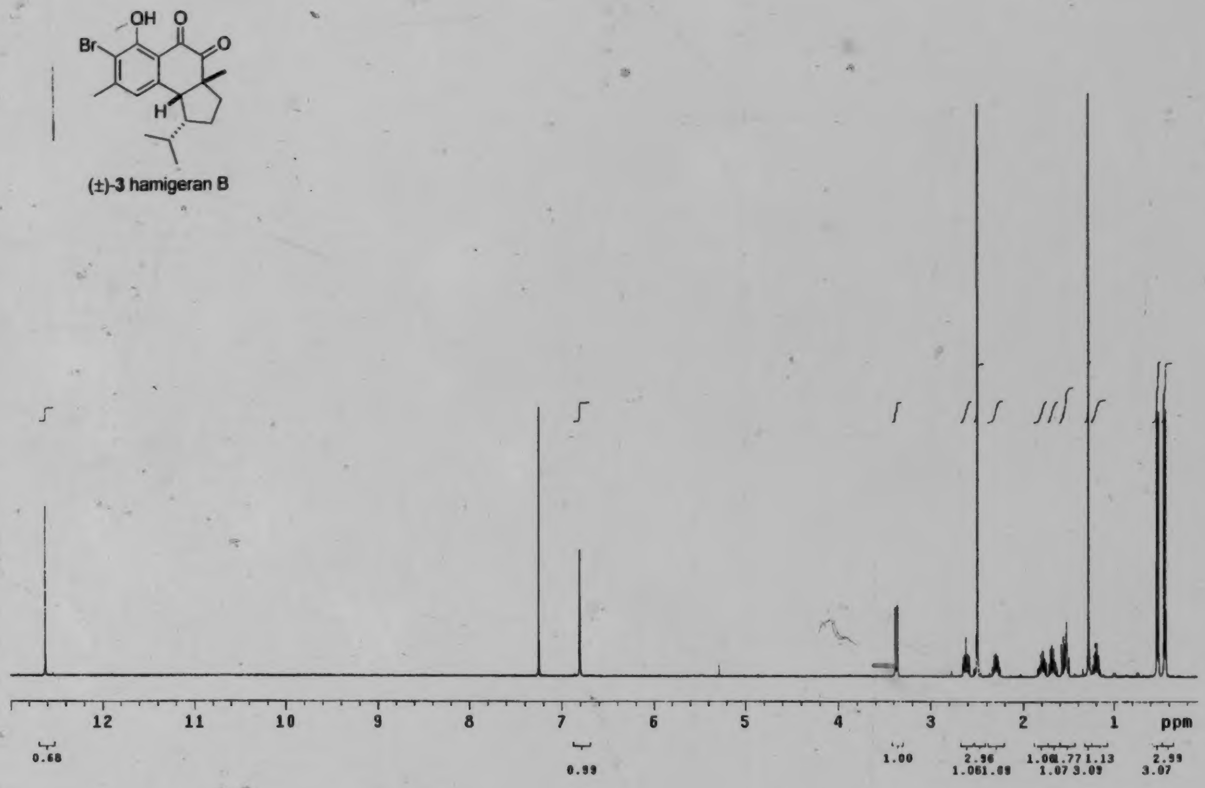
Sample JW-09-201-5
date:Mar 5 2003 seqfil:s2pul hz/mm:21.53 sweep width[Hz]:6983 spectrometer:i400 file:exp
acq.time[s]:2.0 relax. time[s]:3.0 dig.res.[Hz/pt]:0.11 # of scans: 16

Pulse Sequence: s2pul


(±)-3 hamigeran B

100 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
C & CH2 same, CH & CH3 opposite side of solvent signal Sample JW-09-201-3
date:Mar 5 2003 seqfil:apt hz/mm:85.44 sweep width[Hz]:26954 spectrometer:i400 file:exp
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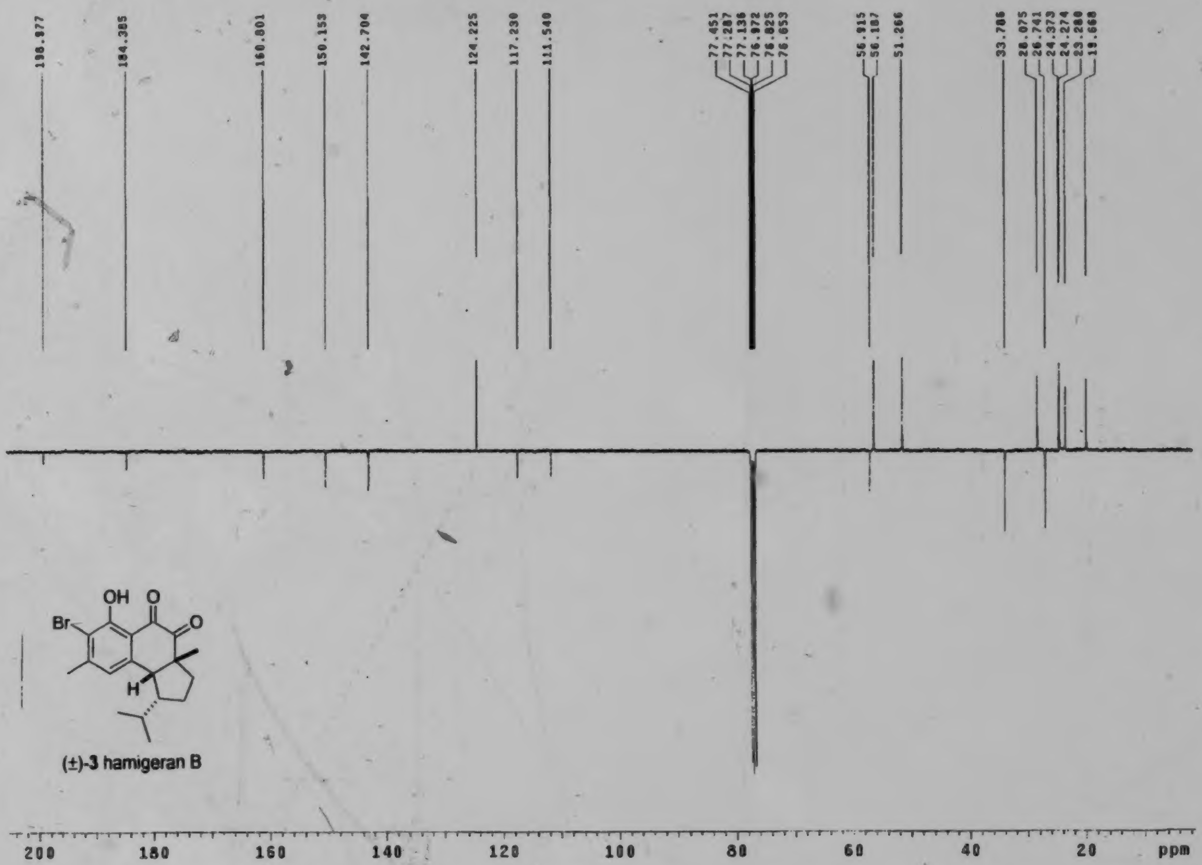
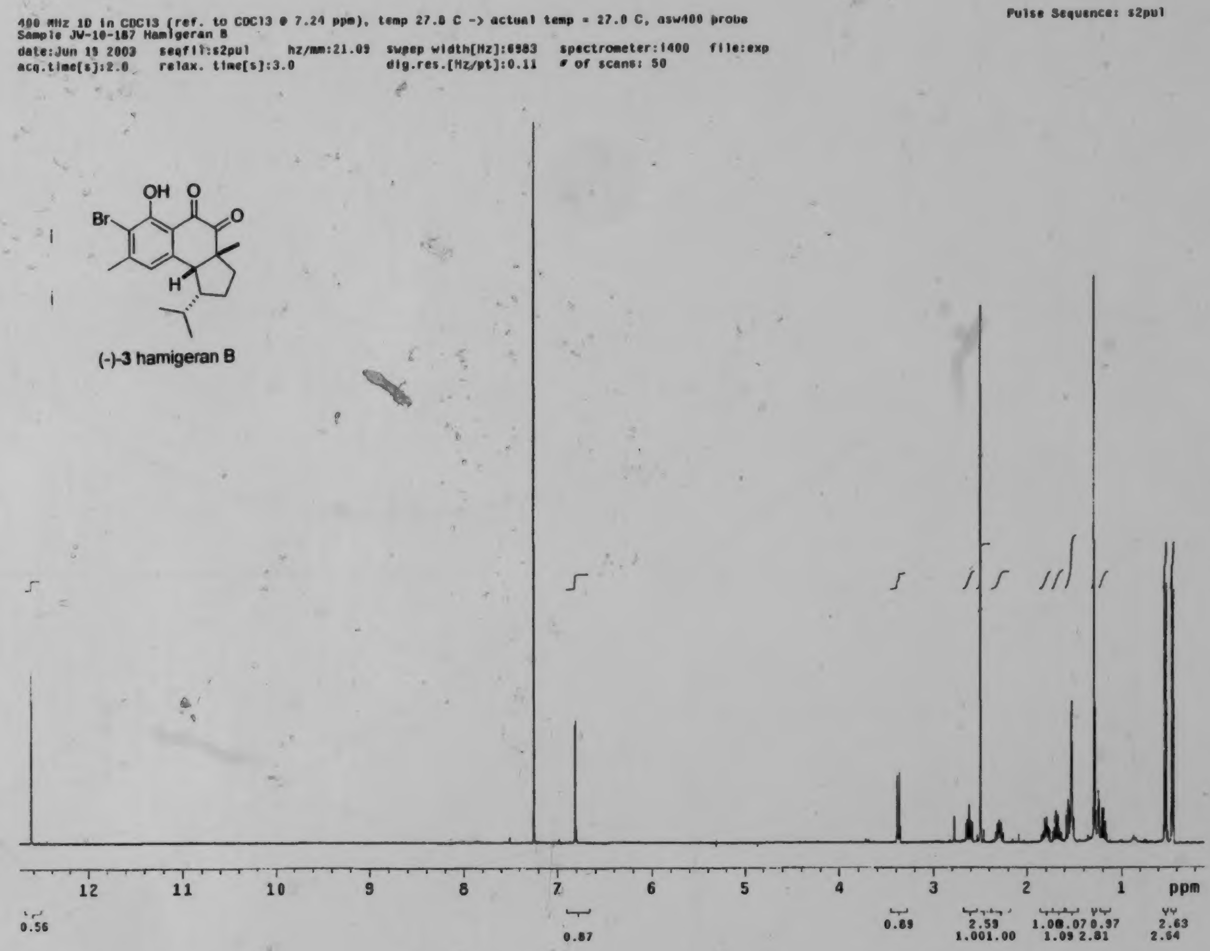
Pulse Sequence: apt



(±)-3 hamigeran B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Sample JW-10-187 Hamigeran B
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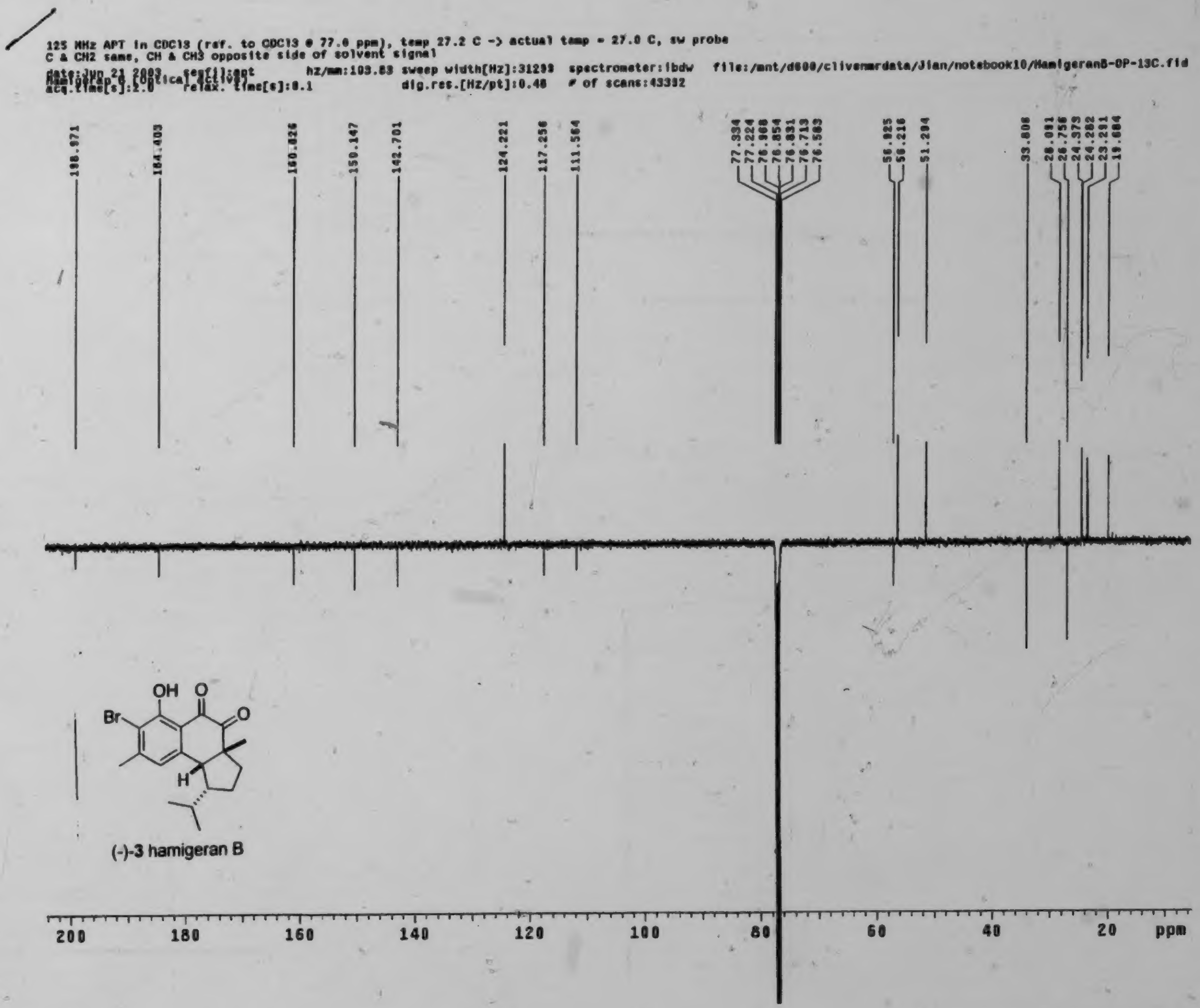
acq.time[s]:2.0 relax. time[s]:3.0 dig.res.[Hz/pt]:0.11 # of scans: 50
Pulse Sequence: s2pul
OH
O
O
Br
H
(-)-3 hamigeran B
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.56
0.87
0.89
2.59
1.001.00
1.08.07
1.09
0.97
2.81
2.63
2.64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C & CH2 same, CH & CH3 opposite side of solvent signal
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Hamigeran B (optical active)
acq.time[s]:2.0 relax. time[s]:0.1 dig.res.[Hz/pt]:0.48 # of scans:43332
198.971
184.403
160.826
150.147
142.701
124.221
117.256
111.564
77.334
77.224
76.968
76.854
76.831
76.713
76.583
56.925
56.216
51.294
33.808
28.091
26.756
24.373
24.282
23.291
19.684
OH
O
O
Br
H
(-)-3 hamigeran B
200
180
160
140
120
100
80
60
40
20
ppm

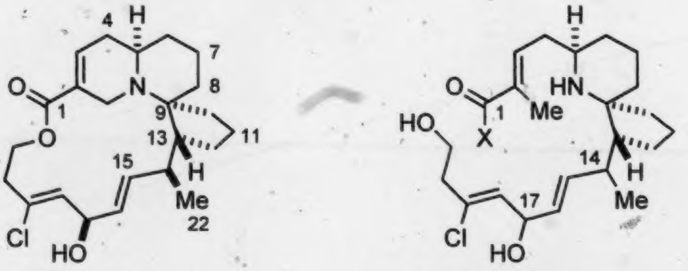
Chapter Three

Studies on the Total Synthesis of Halichlorine and Pinnaic Acid

I Introduction

1.1 General

In their search for biologically active substances from marine organisms, Uemura *et al.*[1] isolated from the marine sponge *Halichondria okadai* Kadata a compound which they called halichlorine (**1**, Scheme 1). This compound was found to be a specific inhibitor of the induction of VCAM-1 (vascular cell adhesion molecule-1) with an IC_{50} of 7 μg/mL.



1

2 X = OH
3 X = $NHCH_2CH_2SO_3H$

Scheme 1

VCAM-1 is a member of the immunoglobulin gene superfamily.[2] It is expressed on the surface of endothelium cells to monitor and regulate leukocyte recruitment into inflamed sites *in vivo*. Because leukocyte infiltration is involved in various allergic inflammatory disorders, as well as pathogenic processes, such as asthma and arteriosclerosis, VCAM-1 has emerged as a potential target for drug discovery. In principle, compounds that inhibit the expression of VCAM-1 could be useful in regulating leukocyte trafficking.

Interestingly, two structurally homologous compounds, pinnaic acid (**2**) and tauropinnaic acid (**3**), were also isolated by Uemura and coworkers from a completely different marine organism, the Okinawan bivalve *Pinna muricata* at the same time.[3] The stereochemistry of **2** is known (see later), and one might assume that **3** has the same stereochemistry. Both pinnaic acid (**2**) and tauropinnaic acid (**3**) are specific inhibitors of cytosolic 85-kDa phospholipase A_2 ($cPLA_2$), an important member of the phospholipase A_2 (PLA_2) family, with IC_{50} values of 0.2 mM and 0.09 mM, respectively.

These kinds of inhibitors are considered to be potential drugs for the treatment of inflammation and other disease states, since PLA_2 is linked to the initial step in the cascade of enzymatic reactions that lead to the generation of inflammatory intermediates.[4] For example, a cytosolic 85-kDa phospholipase A_2 exhibits specificity for the release of arachidonic acid (this acid can mediate the biosynthesis of eicosanoids, prostaglandins, leukotrienes and thromboxanes) from membrane phospholipids.[5]

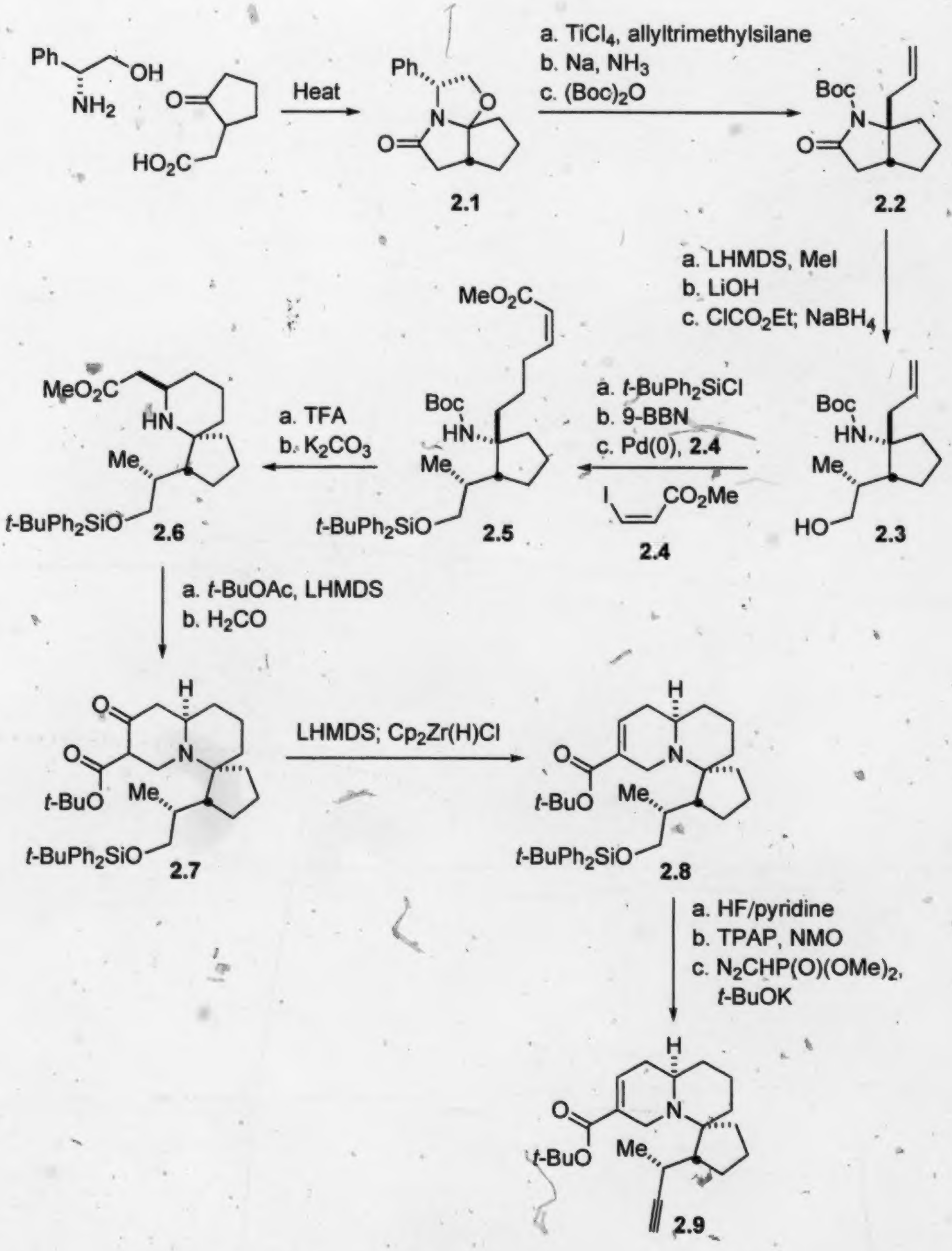
Halichlorine contains a quinolizidine nucleus with a spiro five-membered ring attached at C(9). Appended to the five-membered ring is a divinyl carbinol side chain that is enclosed in a 15-membered macrolactone. Carbons C(9), C(13) and C(14) are contiguous stereogenic centers. Pinnaic acid has the same carbon skeleton as halichlorine except for the tetrahydropyridine ring and the macrolactone. The relative stereochemistry of these compounds was originally established by NMR methods, except for the configuration at C(17) of pinnaic acid (**2**). These studies also tentatively suggested that the C(14) methyl groups of halichlorine and pinnaic acid are epimeric to each other. Later, the absolute stereochemistry of halichlorine was determined by degradation studies.[6] Due to a lack of sufficient material for degradation studies, the absolute stereochemistry of pinnaic acid was not confirmed. However, the stereochemistry of natural pinnaic acid was later assigned by the Danishefsky group[7] during the course of their total synthesis – the configurations at C(14) and C(17) are the same as in halichlorine.

Due to their interesting biological profile and unusual structural features, these compounds have attracted considerable interest among organic chemists. A number of publications related to synthetic studies on these compounds have appeared since 1999, and these studies are summarized in the following sections.

1.2 Total synthesis of halichlorine and pinnaic acid the by the Danishefsky group.

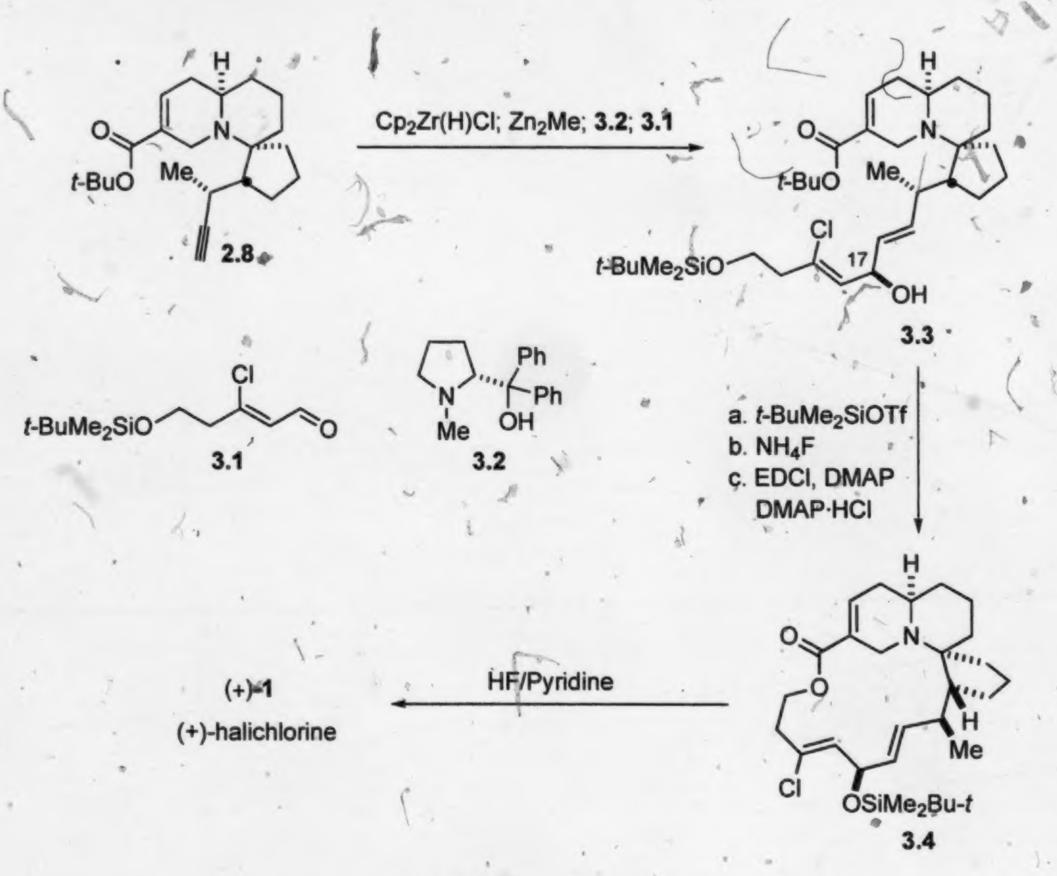
The first total synthesis of (+)-halichlorine was reported by Danishefsky *et al.* in 1999.[8] Their synthesis began with a Lewis acid catalyzed allylation of the known Meyers lactam **2.1** so as to install the quaternary center with stereo control (**2.1** → **2.2**, Scheme 2). After reductive cleavage (Na, NH_3) of the chiral auxiliary and protection of the amide nitrogen, the lactam was alkylated with MeI. The cup-like structure of **2.2** caused alkylation to take place only from the convex face, and so the methyl group was introduced with the required stereochemistry.

The lactam was then hydrolyzed and the released carboxyl group was reduced, to afford alcohol **2.3**. After protection of **2.3**, the allyl group was homologated by using hydroborative Suzuki coupling with (*Z*)-iodoacrylate (**2.4**) to give **2.5**. Next, the amino protecting group was removed under acidic conditions and, after basification, the free amine underwent *in situ* stereoselective Michael addition to the alkenoate, forming the fused piperidine ring system **2.6**.



Scheme 2

The required tetrahydropyridine ring was then formed by a two-carbon chain extension of **2.6**, using a cross Claisen condensation (*t*-BuOCOMe, LHMDS), followed by ring closure via a Mannich reaction with formaldehyde (**2.6** → **2.7**). The remaining β-carbonyl group was removed by treatment with LHMDS and $Cp_2Zr(H)Cl$ to give **2.8**. The silyl ether was cleaved and the resulting alcohol was oxidized and then homologated by one carbon to afford acetylene **2.9**. This tricyclic compound contains four of the five stereogenic centers present in halichlorine.



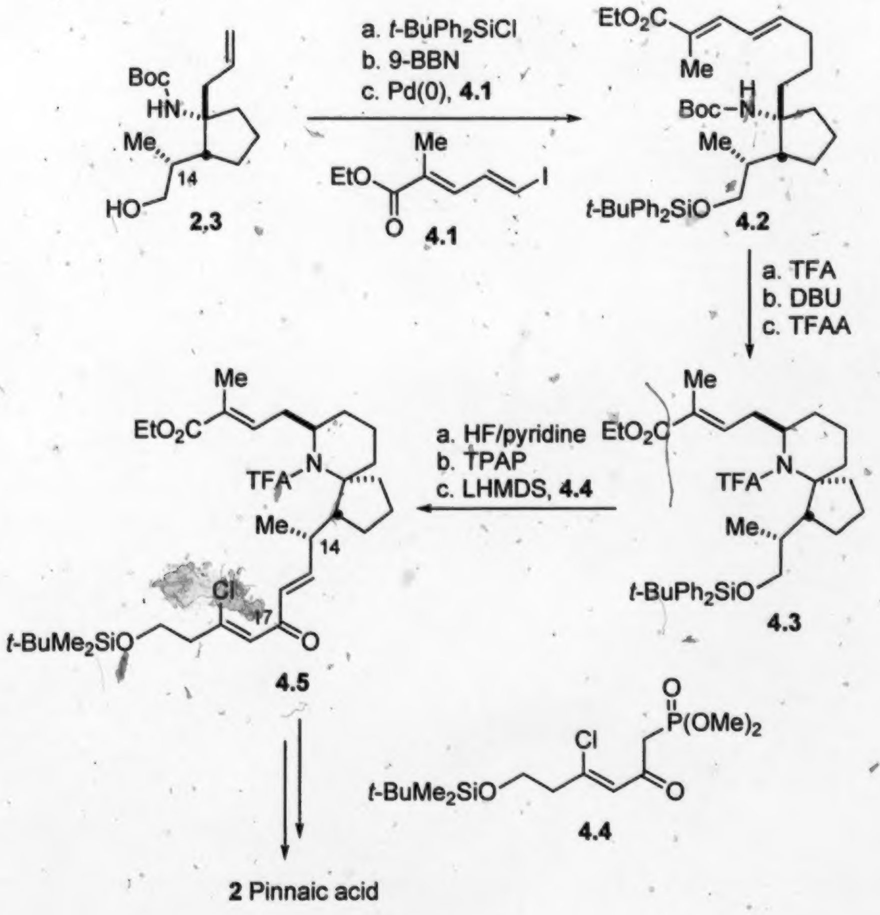
Scheme 3

Now the stage had been set to build up the side chain and to attempt a macrolactonization (Scheme 3). Acetylene

2.8 was converted into an organozinc species, which, in the presence of the external chiral amino alcohol **3.2**, added stereoselectively to aldehyde **3.1** to give a 4:1 mixture of the allylic alcohol **3.3** and its C(17)*S* isomer. Treatment of compound **3.3** with *tert*-butyldimethylsilyl triflate (TBSOTf) generated the corresponding silyl ester of the carboxylic acid while protecting the C(17) alcohol. The protecting groups on the carboxyl and primary alcohol functions were selectively cleaved, and the macrolactonization was then carried out by using Keck's conditions (**3.3** → **3.4**). Finally, deprotection of the C(17) alcohol completed the total synthesis of (+)-halichlorine (**1**).

Starting from compound **2.3**, the Danishefsky group also completed the total synthesis of pinnaic acid.[7,9] As shown in Scheme 4, protection of alcohol **2.3** as its *t*-butyldiphenylsilyl ether, and homologation of the allyl group by using hydroborative Suzuki coupling with vinyl iodide **4.1** gave **4.2**. Next, the amino protecting group was removed under acidic conditions and, after basification, the free amine underwent *in situ* stereoselective intramolecular vinylogous Michael type addition (1,6-addition) to afford the fused piperidine ring system **4.3** with the desired stereochemistry at the newly-created asymmetric center.

The terminal silyl ether was cleaved as usual, and the resulting alcohol was then oxidized and homologated with the known phosphonate **4.4** to furnish **4.5**. Reduction of the C(17) carbonyl gave access to both C(17) stereoisomers. Cleavage of the silyl ether, trifluoroacetyl and ethyl ester functions produced two pinnaic acids that only differed at C(17). The Danishefsky group also managed to use the C(14) epimer of **2.3** as starting material; they applied the same reaction sequences and were able to obtain another two pinnaic acids.



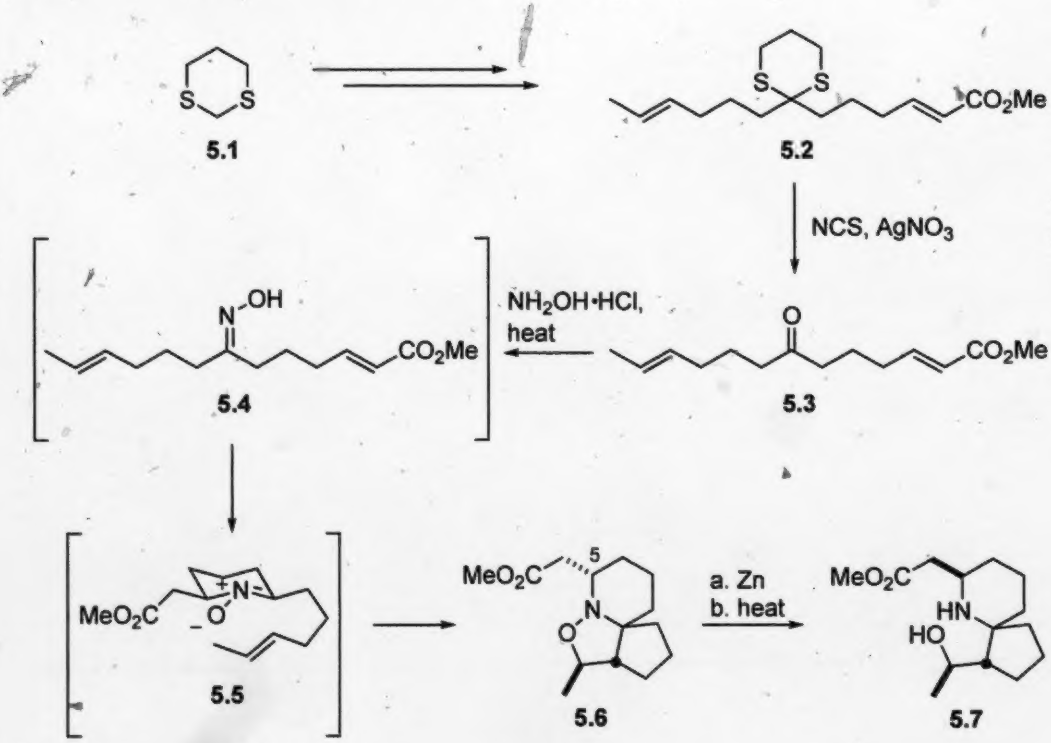
Scheme 4

The NMR spectra of these four synthetic pinnaic acids were then compared to the spectrum obtained from the natural product; as expected, the data for only one synthetic sample completely matched the data for the natural compound. After degradation studies of certain synthetic intermediates, it was then possible to assign the stereochemistry of natural pinnaic acid as 14*S*,17*R* (i.e.

the same as for halichlorine).

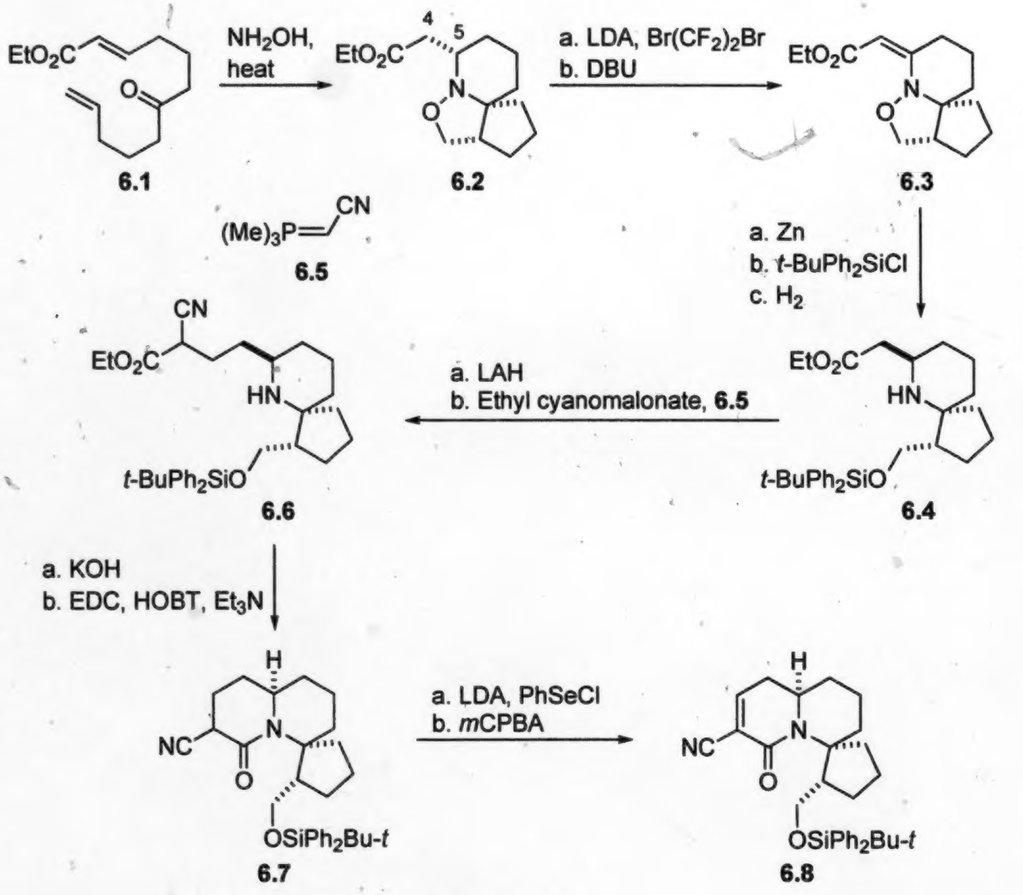
1.3 Synthesis of the azaspirocyclic core structure by the Zhao group.

Zhao *et al.* reported their approach to the azaspiro core structure of halichlorine and pinnaic acid in two different papers at the same time.[10,11] The content of both papers is almost the same.



Scheme 5

Their synthesis was based on sequential Michael addition and intramolecular [3 + 2] nitrone cycloaddition (Scheme 5). Enolate **5.2** was synthesized by dialkylation of 1,3-dithiane (**5.1**). The dithiane was then oxidatively cleaved by *N*-chlorosuccinimide (NCS) and $AgNO_3$ to give ketone **5.3**. Heating this ketone with hydroxylamine hydrochloride and AcONa generated a transient oxime **5.4**, which underwent Michael addition of the nitrogen to the unsaturated ester unit to form nitrone **5.5**. This nitrone underwent cycloaddition *in situ* to afford the tricyclic compound **5.6**, which has all the required stereochemistry except that at C(5). This center was epimerized after reductive cleavage of the N-O bond, via a retro-Michael addition, followed by an intramolecular Michael addition, to give the thermodynamically favored isomer **5.7**; this represents the core structure of both halichlorine and the pinnaic acids.



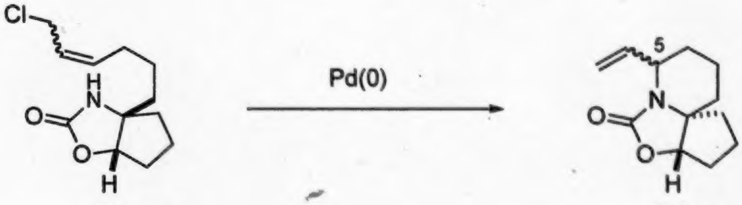
Scheme 6

1.4 Synthesis of the tricyclic halichlorine core by the Shishido group.

In work similar to Zhao's approach, Shishido reported[12] a route to the halichlorine core utilizing the same strategy of tandem Michael addition and nitrone [3 + 2] cycloaddition.

As shown in Scheme 6, the stereochemistry at C(5) was initially the undesired stereochemistry and epimerization was required. This change was carried out by first creating the C(4)-C(5) double bond (**6.2** → **6.3**), followed by reductive opening of the N-O bond, protection of the free hydroxyl functionality and then hydrogenation from the underface so as to set the required stereochemistry (**6.3** → **6.4**). Introduction of the C(4)-C(5) double bond was done by bromination and subsequent dehydrobromination of **6.2**.

Ester **6.4** was reduced and then homologated with ethyl cyanomalonate to afford **6.6**. The last ring was generated by an intramolecular acylation to give amide **6.7**. Desaturation of **6.7** by the standard selenoxide elimination method produced the tricyclic lactam **6.8** as the core of halichlorine.



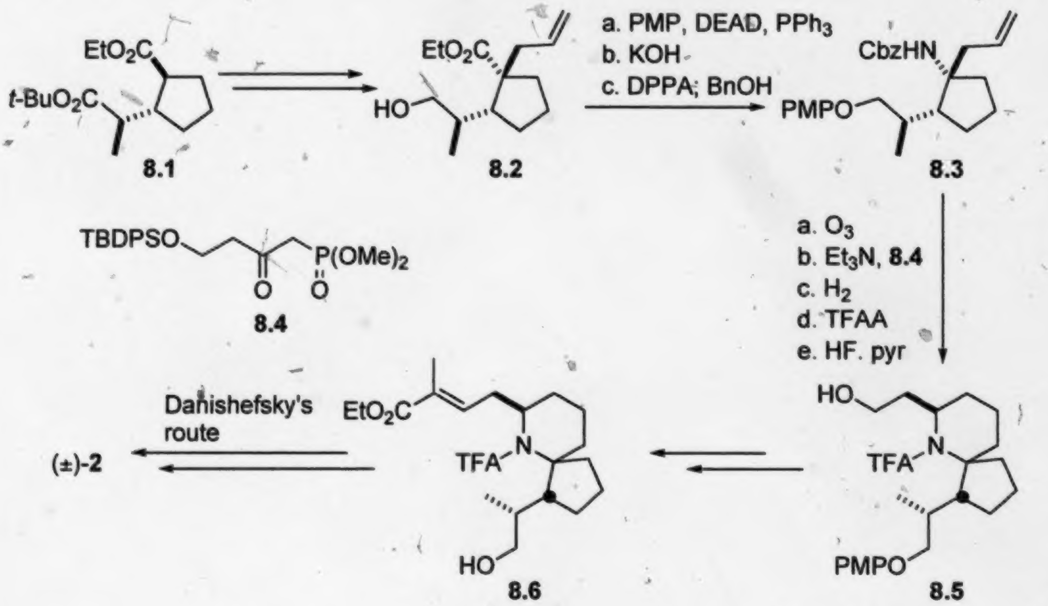
7.1 **7.2**

Scheme 7

Later on, the same laboratory also reported[13] another approach to the bicyclic core, based on a Pd-mediated cyclization (Scheme 7). However, treatment of allyl chloride **7.1** with a Pd(0) catalyst gave only a mixture of C(5) epimers (**7.2**), and the authors are still looking for a way to improve the diastereoselectivity. Compound **7.2** was not elaborated much further.

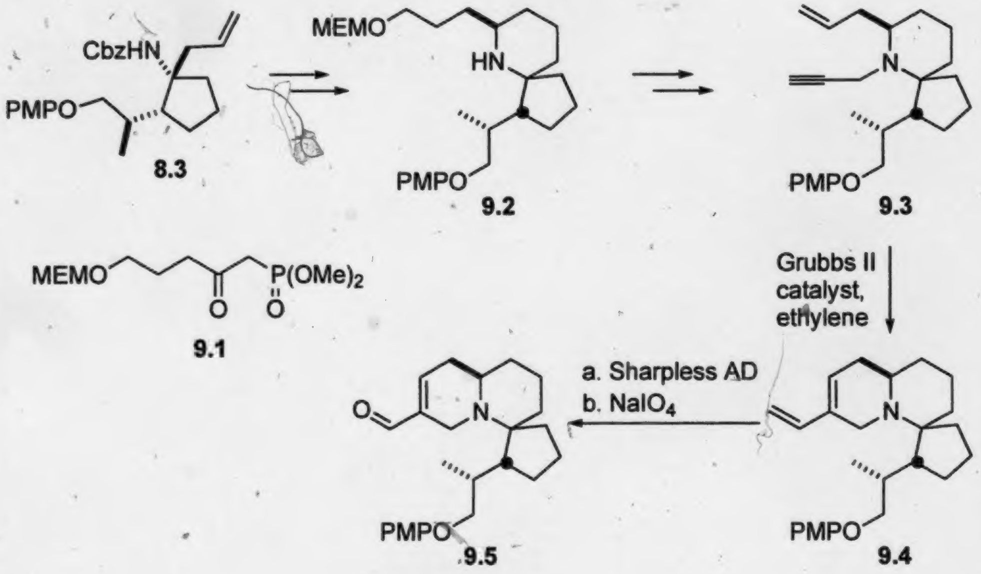
1.5 Synthesis of pinnaic acid and the tricyclic core of halichlorine by the Arimoto group.

Targeted upon the original stereochemical assignment, Arimoto *et al.* reported an asymmetric synthesis of the spirocyclic core of pinnaic acid (**2**).[14] After Danishefsky revised the originally-assigned stereochemistry of **2**,[7] the Arimoto group modified their original route so as to complete a formal synthesis[15] of the natural product.



Scheme 8

The known racemic diester **8.1** could be easily converted into alcohol **8.2** by selective removal of the *t*-butyl group, stereoselective allylation and reduction of the carboxyl group (Scheme 8). The primary alcohol was then protected as its *p*-methoxyphenyl ether. After hydrolysis of the ethyl ester, the resulting carboxyl was subjected to Curtius rearrangement, followed by addition of benzyl alcohol to give the desired Cbz-protected amine (**8.2** → **8.3**). The terminal alkene of **8.3** was cleaved by ozonolysis and homologated with phosphonate **8.4**. At this stage, catalytic hydrogenation brought about a cascade of reactions and built up the spirobicyclic skeleton. *N*-Protection of the resulting cyclic amine with $(CF_3CO)_2O$, followed by deprotection of the terminal silyl ether originally present in **8.4**, afforded compound **8.5**. The alcohol was oxidized to the corresponding aldehyde. Finally, homologation of this aldehyde and deprotection of the *p*-methoxyphenyl ether afforded alcohol **8.6**, the appropriate enantiomer of which had served as a key intermediate in Danishefsky's total synthesis.

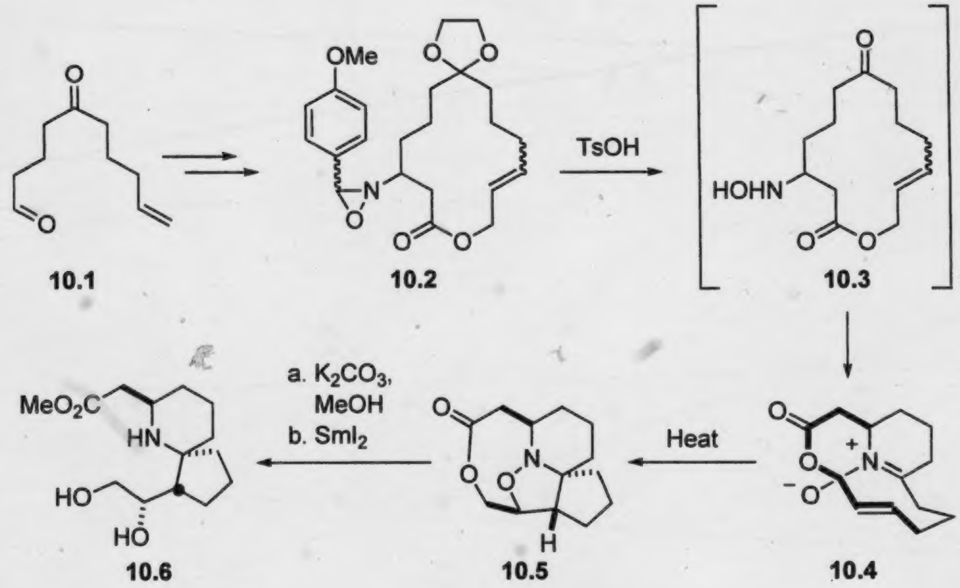


Scheme 9

Starting from alkene **8.3**, the Arimoto group also managed to make the tricyclic core structure of halichlorine.[16] As shown in Scheme 9, applying the same reaction sequence on **8.3** as they had used in the formal synthesis of pinnaic acid, except that phosphonate **9.1** was employed, they were able to obtain amine **9.2**. At this point a propargyl group was attached to the nitrogen atom, and deprotection of the MEM ether gave an alcohol which was then converted into a terminal alkene (**9.2** → **9.3**). Ene-yne **9.3** was heated at reflux in PhMe with Grubbs II catalyst to furnish diene **9.4**. The terminal double bond was then selectively cleaved by dihydroxylation with the Sharpless AD-mix-β, and then oxidative cleavage with $NaIO_4$. This sequence gave racemic aldehyde **9.5** as the tricyclic core of halichlorine.

1.6 Synthesis of the spirocyclic core by the White group.

A synthesis of the spirocyclic core of halichlorine and the pinnaic acids was reported by White *et al.*[17] This work is based on a transannular nitrone cycloaddition. The nitrone precursor **10.2** (Scheme 10) could easily be made from 5-oxo-9-decenal (**10.1**) in about 10 steps. Treatment of **10.2** with *p*-toluenesulfonic acid resulted in simultaneous hydrolysis of the ketal and the oxaziridine to give transiently keto hydroxylamine **10.3**. The latter underwent intramolecular condensation to produce nitrone **10.4**. Thermolysis of **10.4** caused transannular nitrone-olefin [3 + 2] cycloaddition to yield tetracyclic compound **10.5**. Finally, base-catalyzed methanolysis, followed by reductive cleavage of the residual isoxazolidine with SmI_2 gave the racemic azaspirocyclic core (**10.6**).



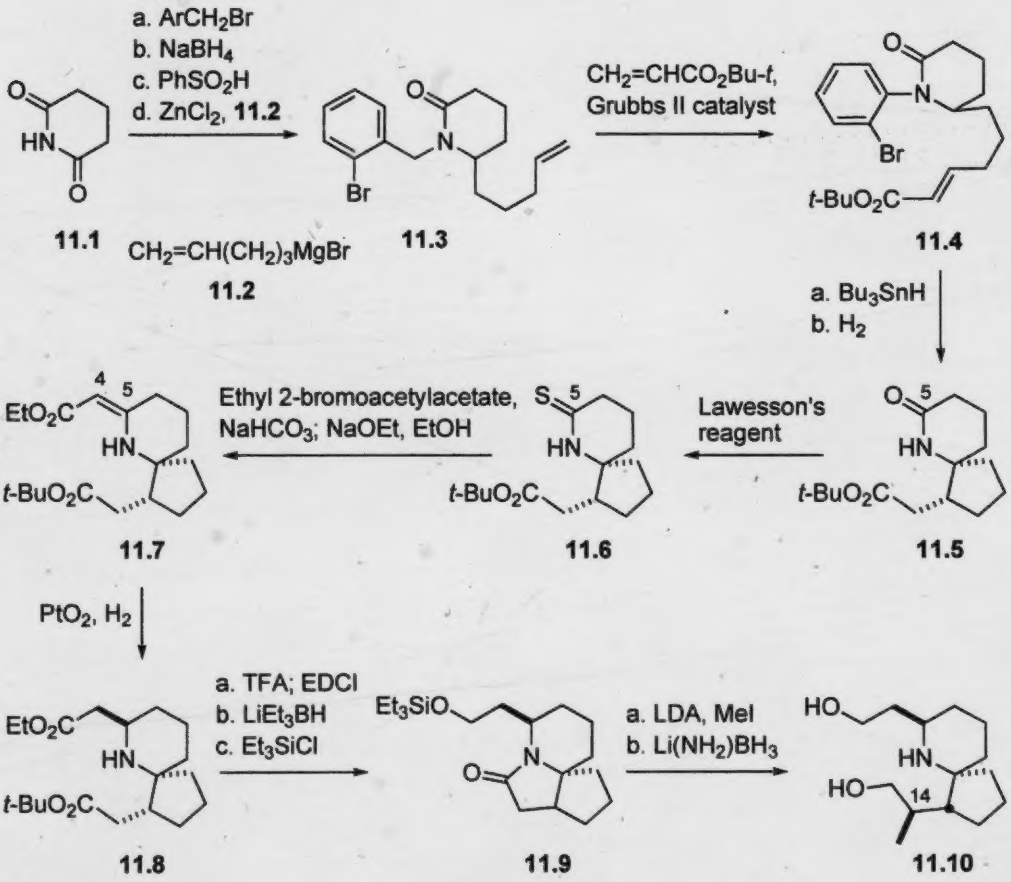
Scheme 10

1.7 Synthesis of the azaspirocyclic nucleus by the Ihara group.

Ihara *et al.*[18] described a novel approach toward the azaspirocyclic framework of halichlorine and pinnaic acids by utilizing a cascade radical translocation and addition process.

Their synthesis started with glutarimide **11.1** (Scheme 11). Alkylation with 2-bromobenzyl bromide, followed by reduction of one of the amide carbonyls and treatment with benzenesulfinic acid, gave a sulfone which was converted into **11.3** by Grignard reaction in the presence of $ZnCl_2$. Cross metathesis with *t*-butyl acrylate afforded the radical precursor **11.4**. This compound then underwent cascade radical translocation and cyclization, and finally, debenzylation by hydrogenolysis produced amide **11.5**.

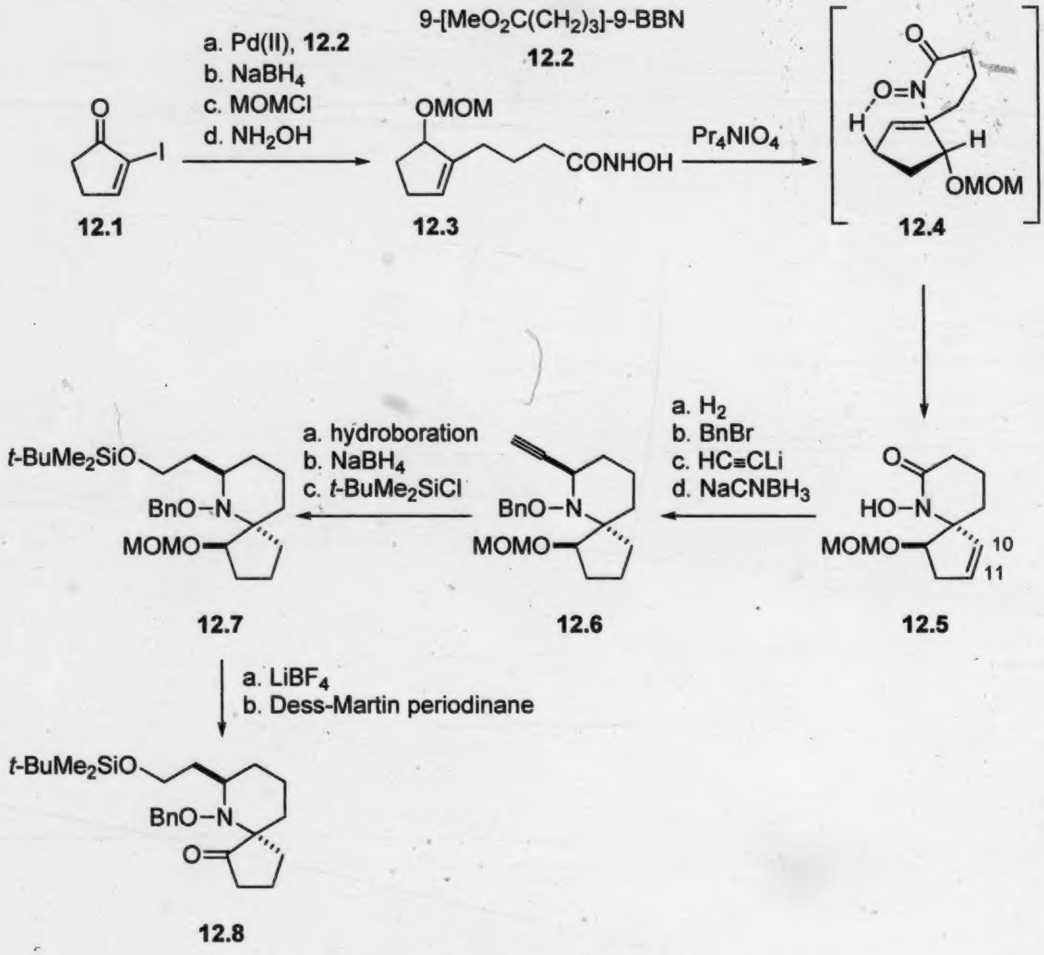
To generate the side chain at C(5), **11.5** was first converted into the corresponding thiolactam **11.6**, and then coupled with ethyl 2-bromoacetoacetate and deacetylated to give **11.7**. Hydrogenation of the C(4)-C(5) double bond furnished ester **11.8**. Selective hydrolysis of the *t*-butyl ester and formation of the five-membered lactam, followed by reduction of the ethyl ester and protection of the resulting alcohol, afforded tricyclic lactam **11.9**. The C(14) methyl could be introduced stereoselectively from the convex face of **11.9**. Treatment of the resulting lactam with Li(NH_2)BH_3 led to reductive lactam opening to give **11.10**, which serves as an advanced intermediate in the synthesis of halichlorine and pinnaic acids.



Scheme 11

1.8 Formal synthesis of halichlorine and pinnaic acid by the Kibayashi group.

In early 2004, Kibayashi *et al.*[19] finished the formal synthesis of both pinnaic acid and halichlorine.

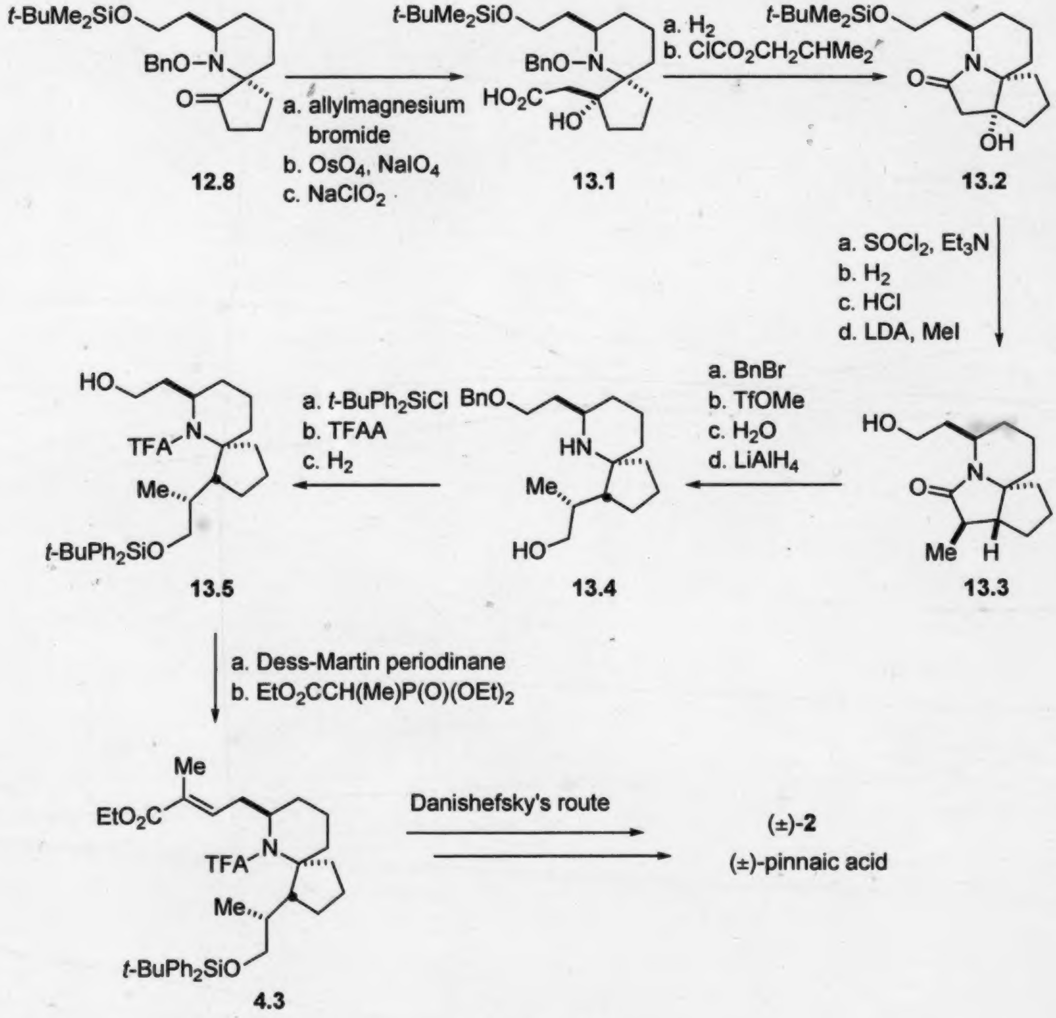


Scheme 12

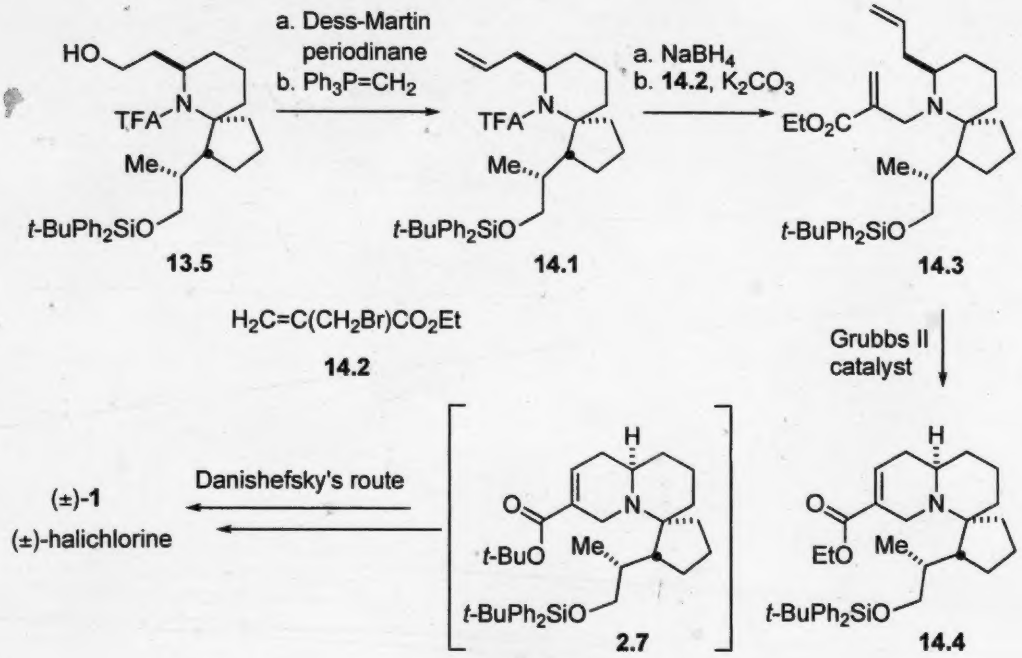
Their synthesis of the azaspirocyclic core structure of halichlorine and pinnaic acid is based on an intramolecular acylnitroso ene reaction.[20] As shown in Scheme 12, in order to make the precursor of the acylnitroso compound – the hydroxamic acid **12.3** – the iodoenone **12.1**, made from 2-cyclopentene-1-one, was first subjected to the Suzuki-Miyaura coupling with the alkylborane unit **12.2**, followed by reduction of the enone, MOM protection of the resulting hydroxyl and treatment with hydroxylamine (**12.1** → **12.3**). Upon oxidation, an intramolecular ene reaction of the *in situ*-generated acylnitroso compound **12.4** proceeded smoothly to yield spirocyclic lactam **12.5**. After saturation of the C(10)-C(11) double bond and benzylation of the *N*-hydroxyl group, the C(5) carbon chain was installed. This was done by treatment with lithium acetylide, followed by reduction with $NaCNBH_3$, to give **12.6**. Hydroboration of the terminal acetylene, followed by $NaBH_4$ reduction of the resulting aldehyde and subsequent silylation afforded compound **12.7**. The MOM ether of **12.7** was cleaved, and oxidation of the resulting alcohol gave the key intermediate **12.8**.

Addition of allylmagnesium bromide to ketone **12.8** (Scheme 13), gave a single adduct. Oxidative cleavage of the double bond and further oxidation with $NaClO_2$ afforded acid **13.1**. Cleavage of the N-O bond, followed by lactam formation, gave tricyclic lactam **13.2**. Dehydration with $SOCl_2$ and subsequent hydrogenation selectively delivered hydrogen from the β face of the lactam. Deprotection of the terminal silyl ether and alkylation, then installed the C(14) methyl – also from the convex face – to give **13.3**. The free hydroxyl was protected and the lactam ring was opened with methyl triflate, followed by hydrolysis and reduction, to furnish amine **13.4**. This alcohol was converted into amide **13.5** by sequential TBDPS protection, *N*-trifluoroacetylation and debenzylation. Dess-Martin oxidation of **13.5** and homologation of the resulting aldehyde provided the Danishefsky intermediate **4.3**.

Because compound **4.3** had been converted into pinnaic acid (**2**) before, the present work constitutes a formal synthesis of racemic **2**.



Scheme 13



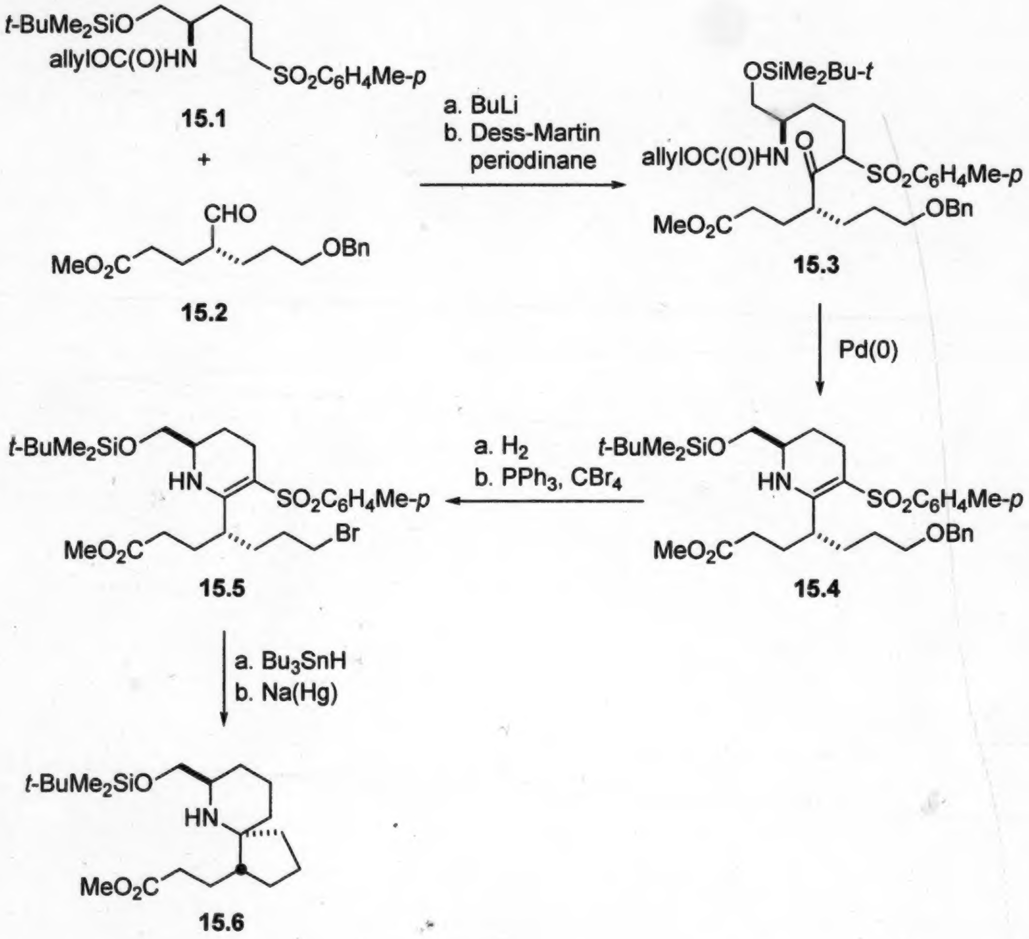
Scheme 14

The advanced intermediate **13.5** was also elaborated in another way so as to complete a formal synthesis of halichlorine. Alcohol **13.5** was converted into olefin **14.1** by Dess-Martin oxidation and homologation (**13.5** → **14.1**, Scheme 14). Treatment of **14.1** with $NaBH_4$, followed by reaction with bromide **14.2** under basic conditions then afforded diene **14.3**. Ring closing metathesis of this compound, mediated by Grubbs II catalyst, furnished **14.4**. This compound is the ethyl ester analogue of the Danishefsky key intermediate **2.7** in the first total synthesis of halichlorine (**1**). Consequently, production of **14.4** could be considered as a formal synthesis of racemic **1**. Kibayashi *et al*. did so consider it, although, strictly speaking, the corresponding *t*-butyl ester should have been made.

II Results and Discussion

2.1 Previous studies in this laboratory.

In this laboratory, an approach to the azaspirocyclic core of halichlorine and pinnaic acid was accomplished by a former member of the group.[21]



Scheme 15

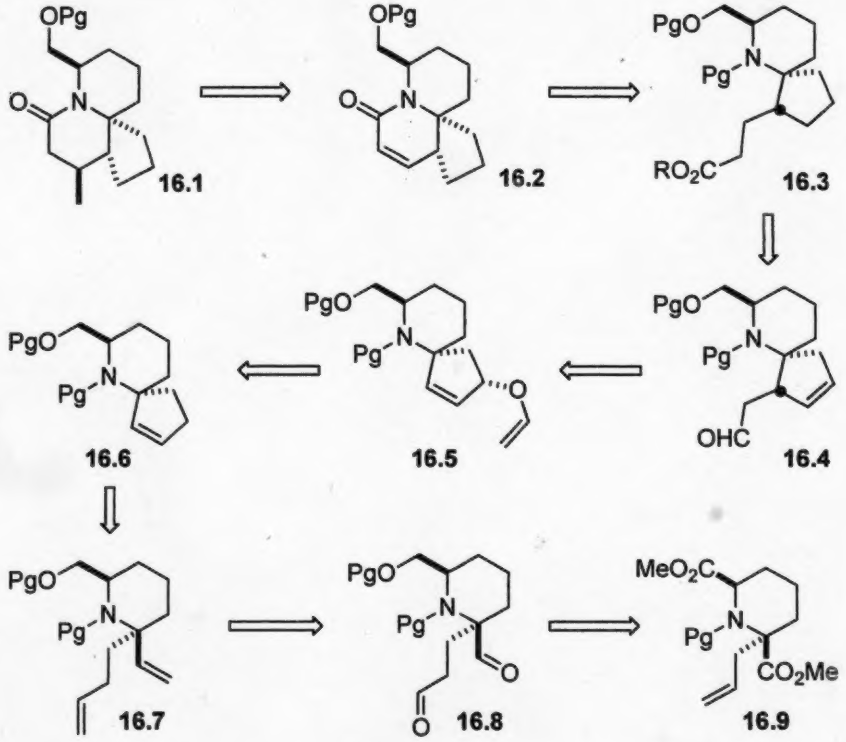
As shown in Scheme 15, the two subunits, **15.1** (made from D-glutamic acid in 10 steps) and aldehyde **15.2** (made from δ-valerolactone in 8 steps), were connected by deprotonation of **15.1**, followed by slow addition of **15.2**. The resulting diastereoisomeric alcohols were oxidized to give ketone sulfone **15.3**. The allyloxycarbonyl group was removed with a Pd(0) catalyst to afford the desired sulfonyl enamine **15.4**. Hydrogenolysis of the *O*-benzyl protecting group and replacement of the liberated hydroxyl by a bromine furnished radical precursor **15.5**. Treatment under standard conditions for radical cyclization, converted this bromide by way of a 5-*exo*-cyclization to the desired spirobicyclic sulfone. Finally, desulfonylation with Na(Hg) gave the 6-azaspiro[4,5]decane **15.6**, representing the core of halichlorine and pinnaic acid.

However, a number of serious difficulties were later encountered while trying to extend this route further. Consequently, the above synthesis was abandoned and a new and more efficient route to the azaspirocyclic core was developed. Because my current work was derived from this approach, a part of those earlier studies will also be discussed in the next section.

2.2 Synthesis of the spirocyclic core by ring closing metathesis and installation of the C(13) carbon chain by Claisen rearrangement.

Our initial target was the tricyclic lactam **16.1** (Scheme 16), which has the same stereochemistry at all four stereogenic centers as halichlorine (**1**) and pinnaic acid (**2**). Our retrosynthetic analysis showed that **16.1** might be derived by stereospecific methylcuprate addition to the unsaturated precursor **16.2**. This, in turn, should be obtainable by lactam formation from the spiro compound **16.3**.

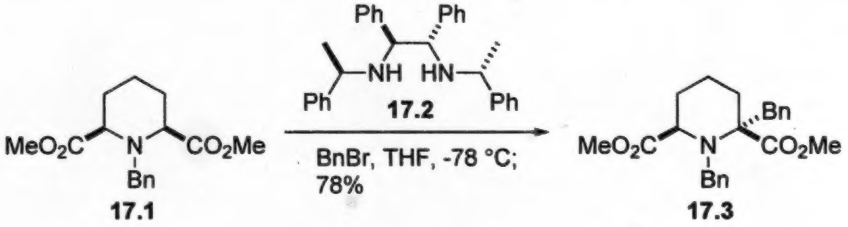
Saturation of the double bond of **16.4** and homologation of the aldehyde functionality would give rise to **16.3**. The structure of **16.4** immediately suggested that it could be made by Claisen rearrangement of vinyl ether **16.5**.



Scheme 16

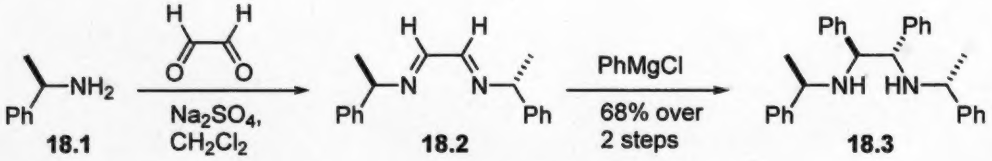
Allylic oxidation of **16.6** and vinyl ether formation would serve to generate **16.5**. We expected that compound **16.6** could be obtained by ring closing metathesis of a diene such as **16.7**. This diene would be available by homologation of dialdehyde **16.8**. To make this dialdehyde, we needed the piperidine diester **16.9**.

To generate diester **16.9**, which bears an asymmetric quaternary center, we decided to follow the Simpkins’s communication,[22] in which the chiral amide **17.2** was used to enantioselectively deprotonate α to one of the ester groups of **17.1**. The resulting enolate was allowed to react with the electrophile BnBr, which approaches from the α face of the piperidine ring to give the alkylated product **17.3** in >98% ee (Scheme 17). A number of related examples were reported in this communication; for some of the products the ee was actually measured, but not for all of them, although it was implied that all examples gave a high ee.

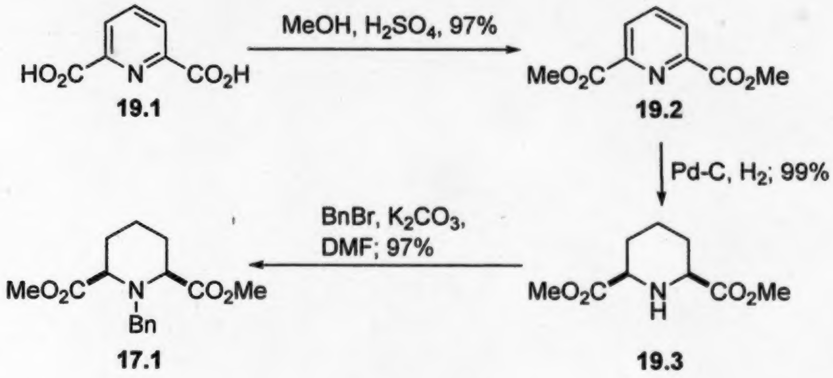


Scheme 17

The chiral diamine **17.2** was prepared from commercially available (*R*)-(+)-α-methylphenylamine (**18.1**) (Scheme 18). Condensation of 2 equiv of **18.1** with one equiv of glyoxal, using Na_2SO_4 as dehydrating agent, gave bisimine **18.2** in nearly quantitative yield.[23] Addition of PhMgCl to **18.2** afforded crystalline diamine **18.3** (68% over 2 steps).[24] Our synthetic material had $[\alpha]_D$ +192°, which was quite close to the reported literature value, $[\alpha]_D$ +205°. The diamine could also be reused after each alkylation reaction by recrystallization.

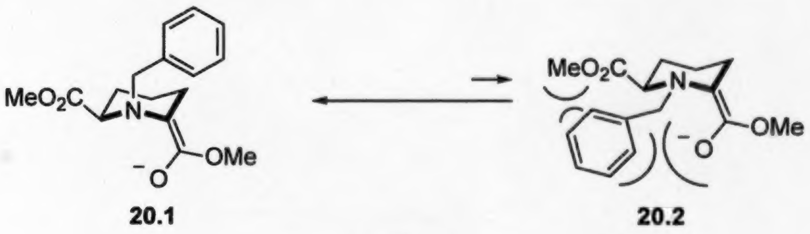


Scheme 18



Scheme 19

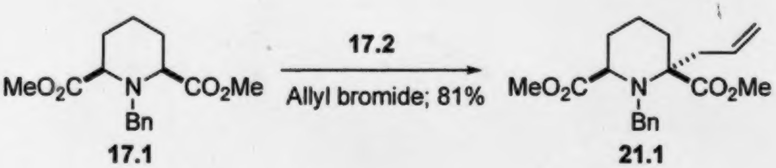
2,6-Pyridinedicarboxylic acid (**19.1**) was esterified by treatment with refluxing MeOH in the presence of catalytic H_2SO_4 (Scheme 19).[25] After basic workup, diester **19.2** was obtained in 97% yield. The pyridine ring was saturated by hydrogenation (50 psi, Pd-C, 99%) to give the *cis*-diester **19.3** exclusively.[26] This amine was then benzylated with BnBr and K_2CO_3 in DMF[27] to give diester **17.1** in high yield.



Scheme 20

The basis of the enantioselectivity in the reaction of diester **17.1** with chiral amide **17.2** has not been proposed, but a reason for the diastereoselectivity in the alkylation has been suggested.[22] Enolate **20.1** was thought to be the major conformation in the reaction, rather than **20.2**. The benzyl group is likely to be disposed on the top face of the piperidine ring to alleviate $A^{1,3}$-strain; hence the top face is shielded from the incoming electrophile.

Following the procedure published by Simpkins,[22] we alkylated diester **17.1** by using the chiral dilithium amide base **17.2** and allyl bromide (1.4 equiv) to give **21.1** in about 60% yield along with 5-10% of a diastereomer that could not be separated by flash chromatography. However, we soon found that if we increased the amount of electrophile to 3 equiv, the reaction was much cleaner, and the desired product could be isolated in 80% yield.



Scheme 21

In their communication, Simpkins assumed that the allylation of diester **17.1** would give **21.1** in 98% ee, based on the fact that a few other alkylations with chiral amide **17.2** all gave 98% ee (chiral HPLC measurement).[22] However, in our hands, while trying to obtain an X-ray crystal structure analysis of compound **26.2** (see later, Scheme 26), we found that our synthetic material did not have the desired high optical purity, and the crystal analyzed was, in fact, of racemic material.

This unexpected result forced us to reevaluate the entire route and a chiral HPLC analysis[28] showed that our compound **21.1** had an ee of about 69%.[29] To try to establish why the alkylation failed to afford the reported ee, we did a few tests on Simpkins' method, as shown in Table 1: First, we repeated the benzylation on the same scale as

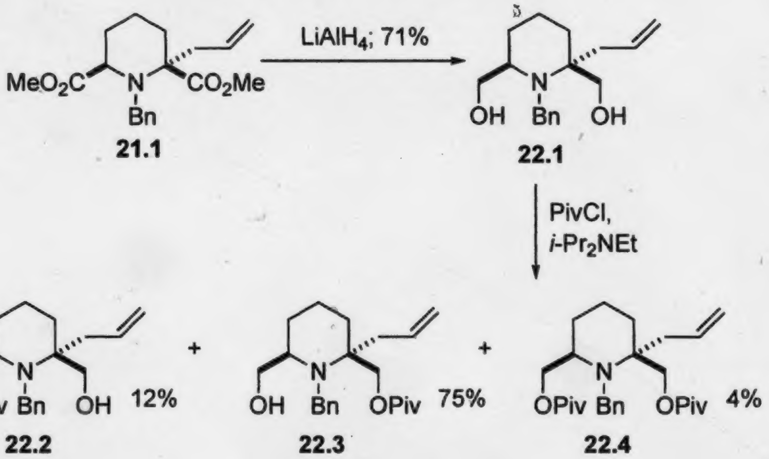
Simpkins *et al.* (entry 1). Our product had $[\alpha]_D$ +32°, which is close to the reported value ($[\alpha]_D$ +27°).[22] Then, we did a small scale alkylation, using allyl bromide as electrophile, and the product **21.1** had $[\alpha]_D$ +40° (Simpkins reported +38°).[30] However, when we did large scale reactions, even with a pre-cooled solution of starting diester (entry 3 and 4), the $[\alpha]_D$ value dropped to +26°. From these results, we concluded that the diastereoselectivity of this reaction is lower in large scale reactions.

Table 1

Entry	Electrophile	Scale of 17.1 (THF)	$[\alpha]_D$ found	$[\alpha]_D$ reported
1	BnBr	100 mg (4 mL)	+32	+27
2	Allyl bromide	110 mg (4 mL)	+40	+38
3	Allyl bromide	5.5 g (20 mL)	+26	
4	Allyl bromide	5.0 g (50 mL)	+26	

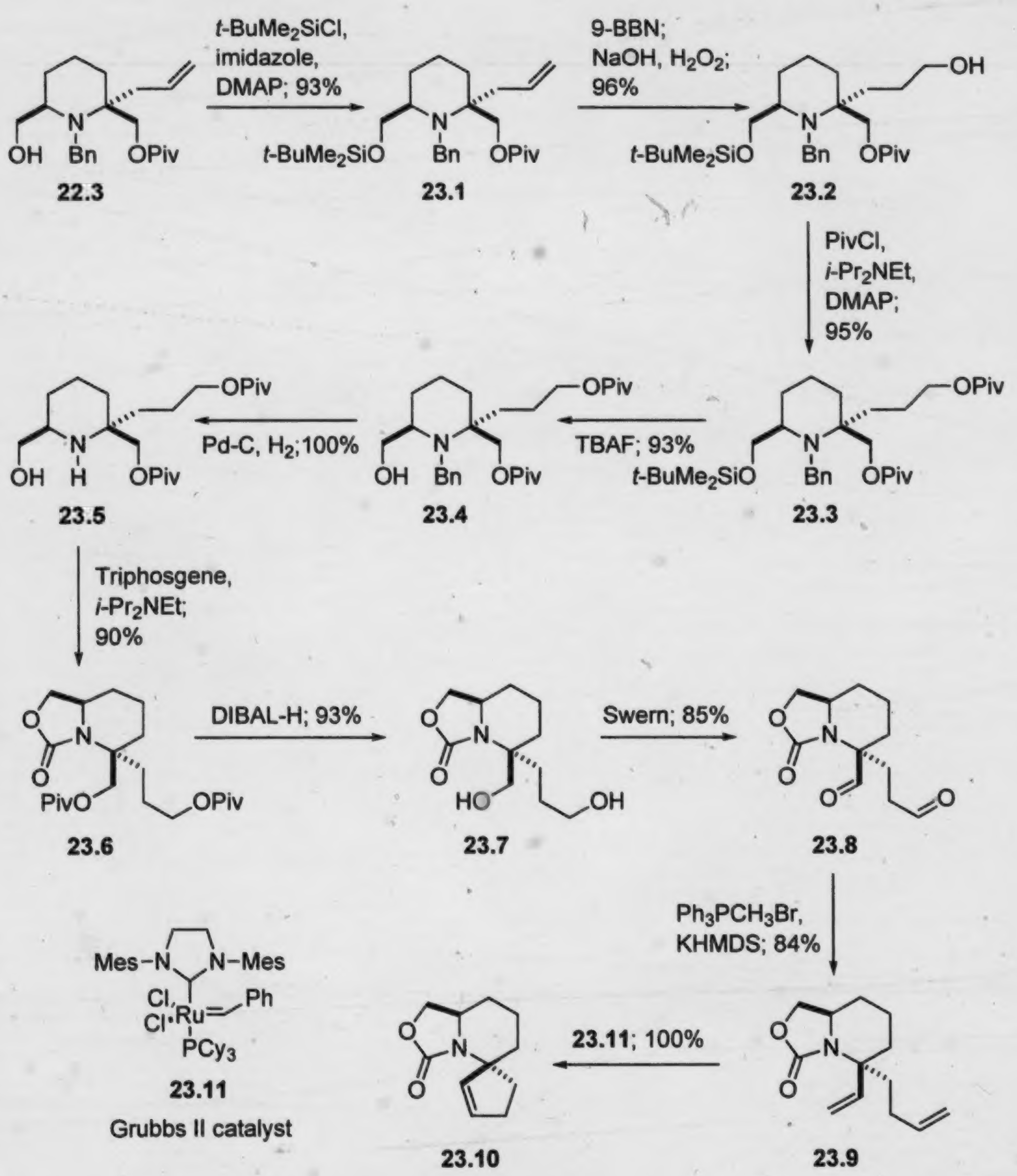
Reaction conditions: entry 1 and 2, addition time of **17.1** ca 5 min
entry 3 and 4, addition time of **17.1** ca 90 min
entry 4, **17.1** solution was precooled to -78 °C

Although we could only obtain **21.1** with 69% ee, we decided to accept this result for the time being. Diester **21.1** was exhaustively reduced with $LiAlH_4$ to give the pure diol **22.1** in 71% yield (Scheme 22). At this stage, the diastereomer resulting from the previous step was separated. The diol could be selectively acylated with *t*-BuCOCl at -10 °C to give **22.3** in 75% yield, along with 12% of the regioisomer (**22.2**) and 4% of doubly esterified product (**22.4**). We could not increase the yield of **22.3** either by changing the addition rate of *t*-BuCOCl or by further lowering the reaction temperature. The structure of **22.3** was assigned by extensive NMR studies.[31]



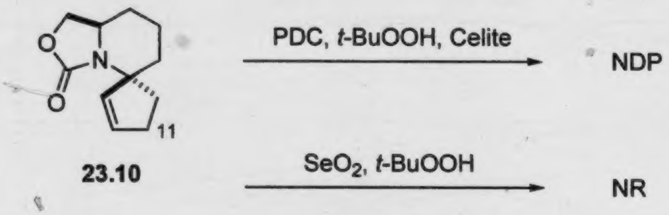
Scheme 22

With the goal of reaching a spirocyclic compound such as **16.6**, we protected the free hydroxyl of **22.3** as it silyl ether (*t*-$BuMe_2SiCl$, imidazole, DMAP, 93%) (**22.3** → **23.1**, Scheme 23).[32] Hydroboration of the terminal double bond with 9-BBN proceeded smoothly to an intermediate alkylborane, which was oxidized *in situ* with NaOH and H_2O_2 to afford alcohol **23.2** in 96% yield. The alcohol was acylated with *t*-BuCOCl in the presence of *i*-Pr_2NEt and DMAP (95%) to give **23.3**, and the silyl ether was then cleaved by TBAF (93%) to produce alcohol **23.4**. Hydrogenolysis of the *N*-benzyl group, using Pd-C and H_2, gave the desired amino alcohol **23.5** in quantitative yield. This compound was acylated with triphosgene to produce carbamate **23.6**, in which both alcohol and nitrogen functionalities are protected.



Scheme 23

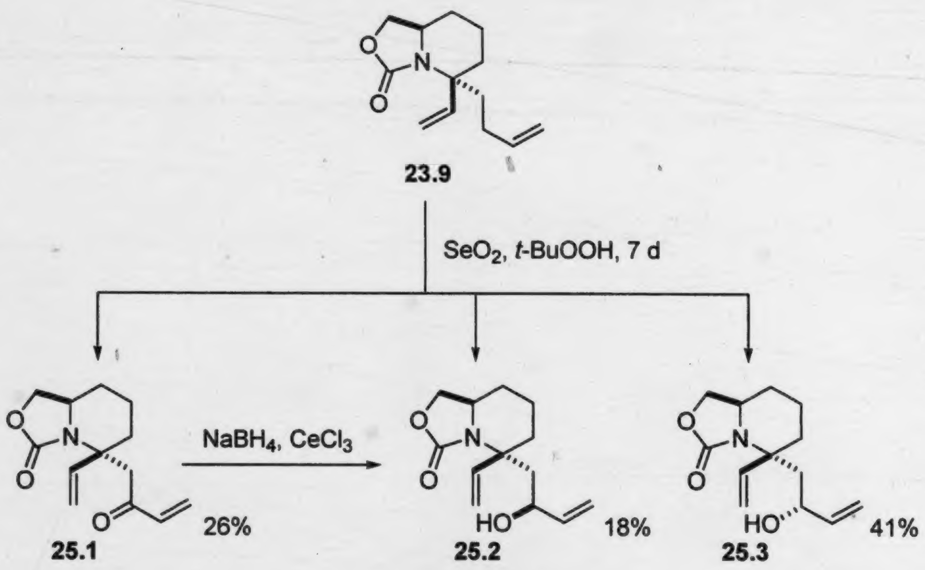
The pivaloyl groups of **23.6** were removed reductively by treatment with excess DIBAL-H so as to release diol **23.7** (93%). Swern oxidation of the diol gave the expected dialdehyde **23.8** in 85% yield, after chromatographic purification. Wittig olefination of this dialdehyde, by treatment with an excess of $Ph_3PH=CH_2$, furnished diene **23.9** (84%). Finally, ring closing metathesis of **23.9**, using the second generation Grubbs catalyst (**23.11**, Scheme 23), afforded spirocyclic compound **23.10** quantitatively.



Scheme 24

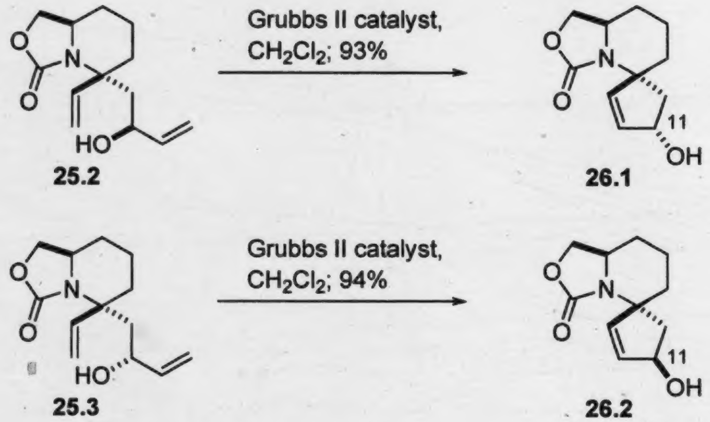
With compound **23.10** in hand, we tried to oxidize the allylic position at C(11), so that we would be able to make a compound such as **16.5** for the planned Claisen rearrangement. We first followed the procedure published by Chandrasekaran *et al.*[33] – treatment of **23.10** with 1:1 PDC-t-BuOOH in the presence of Celite (Scheme 24). Unfortunately, this did not give any trace of the desired product, and no starting material could be recovered from the reaction mixture. In addition, SeO_2-t-BuOOH oxidation[34] produced no reaction at all even after a reaction time of 5 days.

Disappointed by the above result, we turned our attention to the diene before the ring closing metathesis. Treatment of diene **23.9** with catalytic SeO_2 in the presence of excess t-BuOOH,[34] using CH_2Cl_2 as solvent at room temperature for 7 days, afforded a separable mixture of three compounds (Scheme 25). Changes of the solvent or an increase in temperature only led to a complex mixture.



Scheme 25

Ketone **25.1**, isolated from the mixture in 26% yield (Scheme 25) could be reduced to the diastereomeric alcohols **25.2** and **25.3** in high yield by treatment with NaBH$_4$ and CeCl$_3$ in MeOH.[35] The identities of these two alcohols were established first by extensive NMR studies, and then by single crystal X-ray analysis of **25.3** (Figure 1).


Grubbs II catalyst, CH2Cl2; 93%
25.2
26.1
11
OH
Grubbs II catalyst, CH2Cl2; 94%
25.3
26.2

Scheme 26

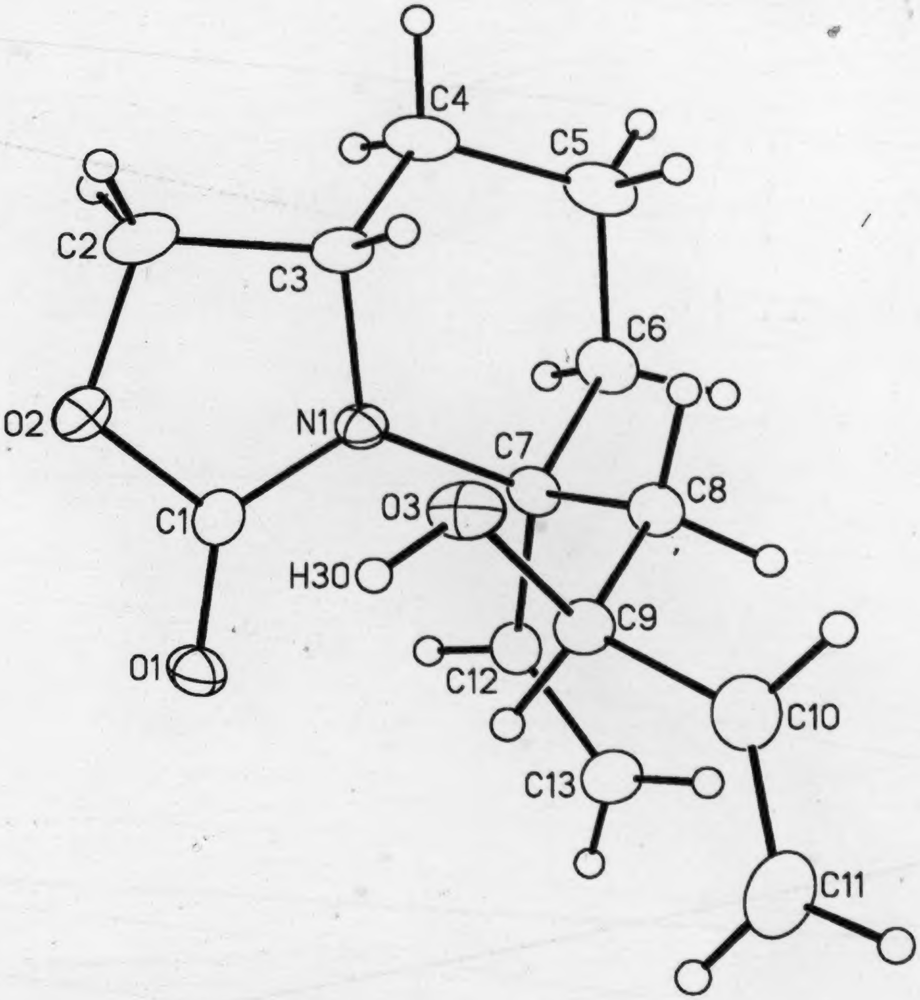


Figure 1 Crystal structure of **25.3**

Both **25.2** and **25.3** underwent ring closing metathesis smoothly with the second generation Grubbs catalyst to give spiro compounds **26.1** and **26.2** in excellent yields (Scheme 26). Here again, the identities of the two C(11) isomeric alcohols were established by single crystal X-ray analysis of **26.2** (Figure 2). It is worth mentioning here that our sample of **26.2** was found to be racemic, and so this is the point at which we found the problem discussed above of the optical purity of the Simpkins alkylation product. We decided to deal with this problem at a later stage.

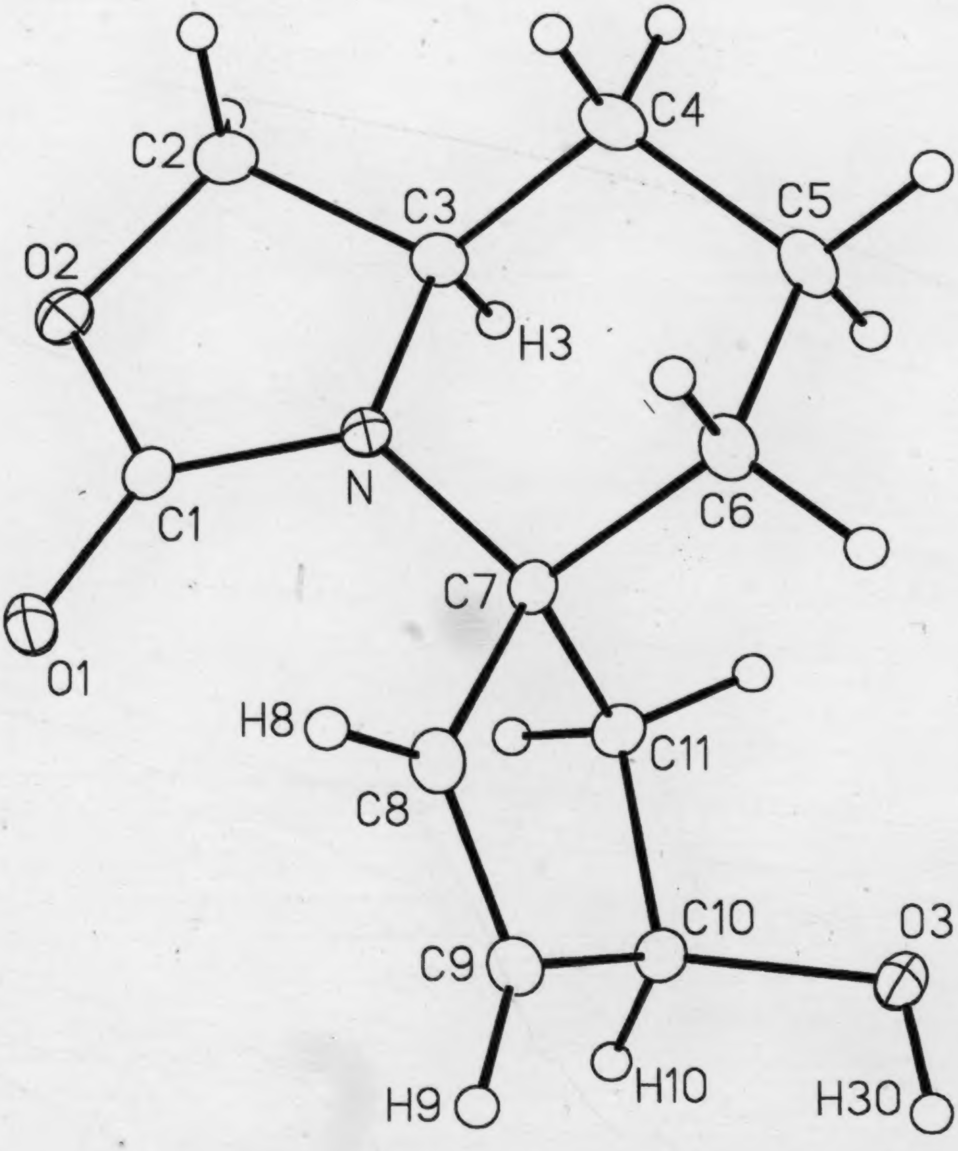
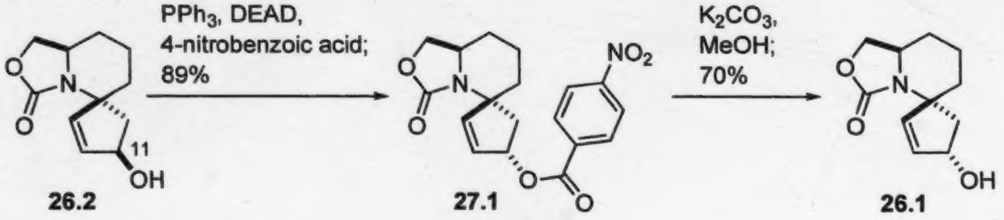
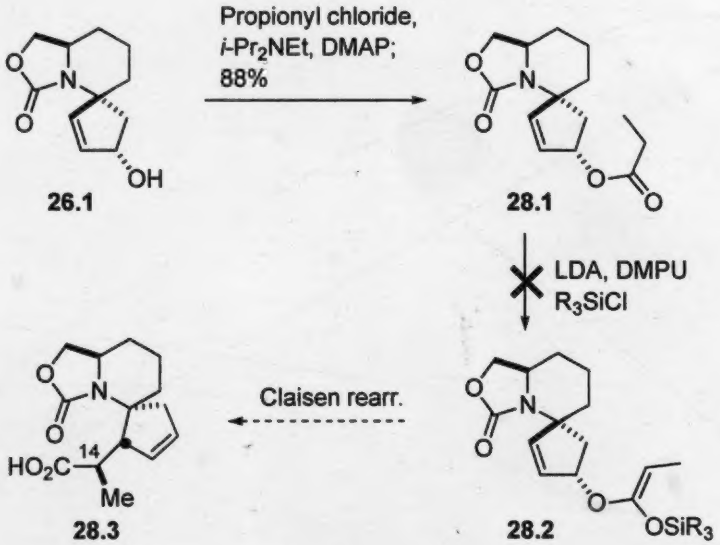


Figure 2 Crystal structure of **26.2**



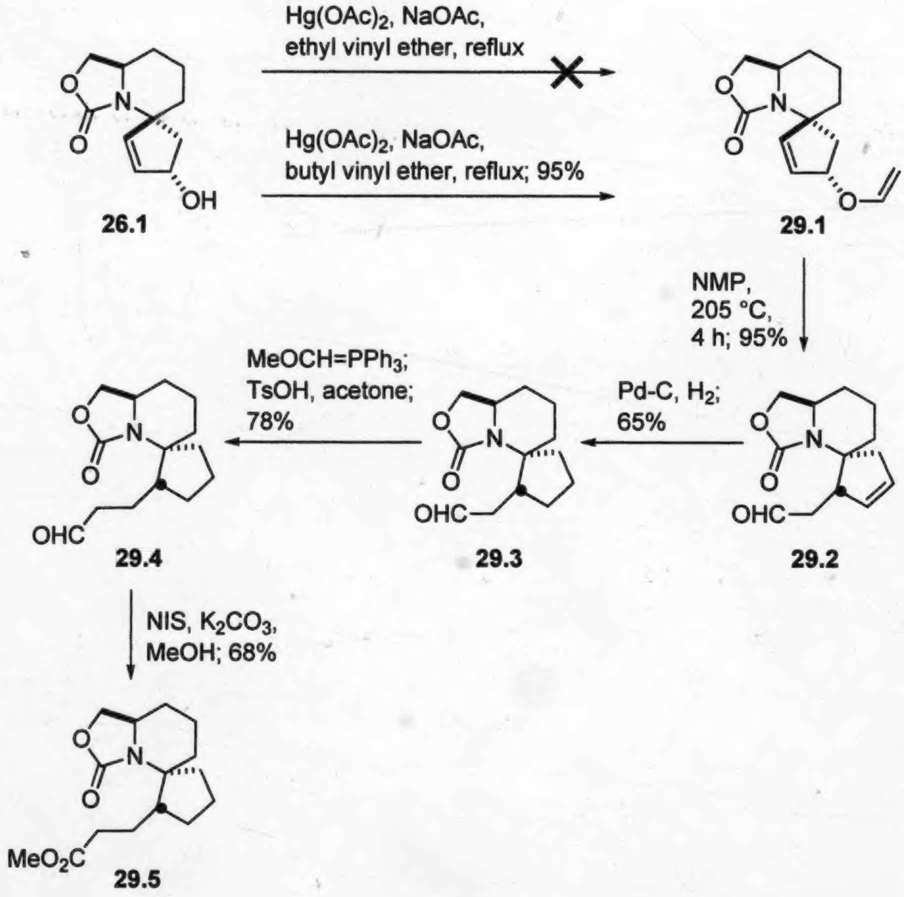
Scheme 27

To obtain the required stereochemistry at C(13) after rearrangement, we needed the 11*S* alcohol **26.1**. Accordingly, the 11*R* alcohol **26.2** was inverted by a modified Mitsunobu protocol[36] (Ph_3P, DEAD, 4-nitrobenzoic acid, benzene, 89%) to afford ester **27.1** (Scheme 27). Hydrolysis of this ester with K_2CO_3 in MeOH gave alcohol **26.1** in 70% yield.



Scheme 28

With **26.1** in hand, the stage had been set for the crucial rearrangement to build the C(13) carbon chain. Guided by the studies Ireland *et al.*[37] on this subject, we first tried the Claisen rearrangement of the (*Z*)-silyl enol ether **28.2** (Scheme 28), in the hope that the rearrangement would occur via a chair-like transition state, and give product **28.3** with desired stereochemistry at both C(13) and C(14). Accordingly, propionate **28.1** was prepared (88% yield) by acylation of the allylic alcohol with EtCOCl. However, we could not make the planned silyl enol ether by treating the derived enolate with either Me_3SiCl or *t*-$BuMe_2SiCl$. We assumed that steric hindrance within the enolate is somehow responsible.

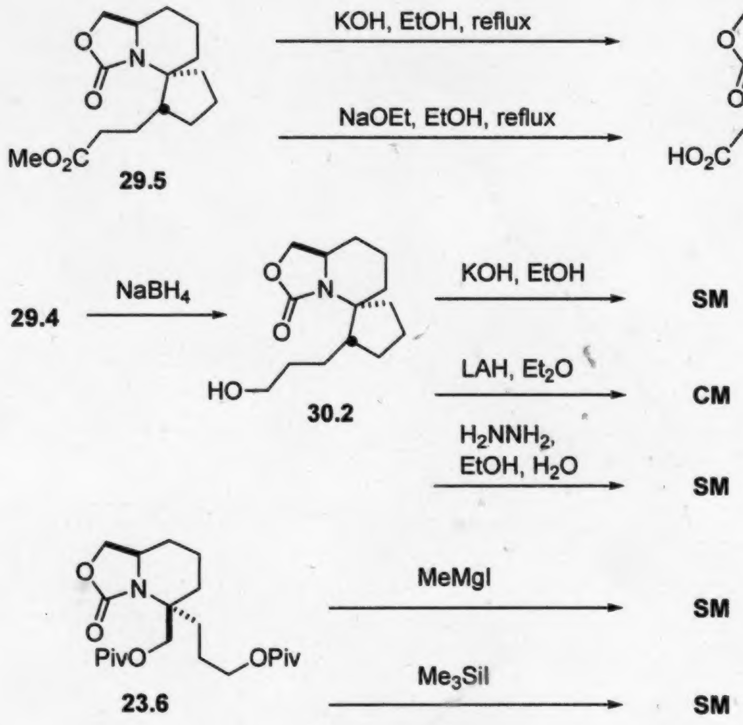


Scheme 29

Therefore, we decided to make the vinyl ether from alcohol **26.1**. Treatment of **26.1** with $Hg(OAc)_2$ and AcONa in ethyl vinyl ether at reflux[38] resulted no reaction at all (Scheme 29). However, when we did this reaction in butyl vinyl ether (bp ca. 20 °C higher), vinyl ether **29.1** could be obtained in 95% yield after a reflux period of 3 days.

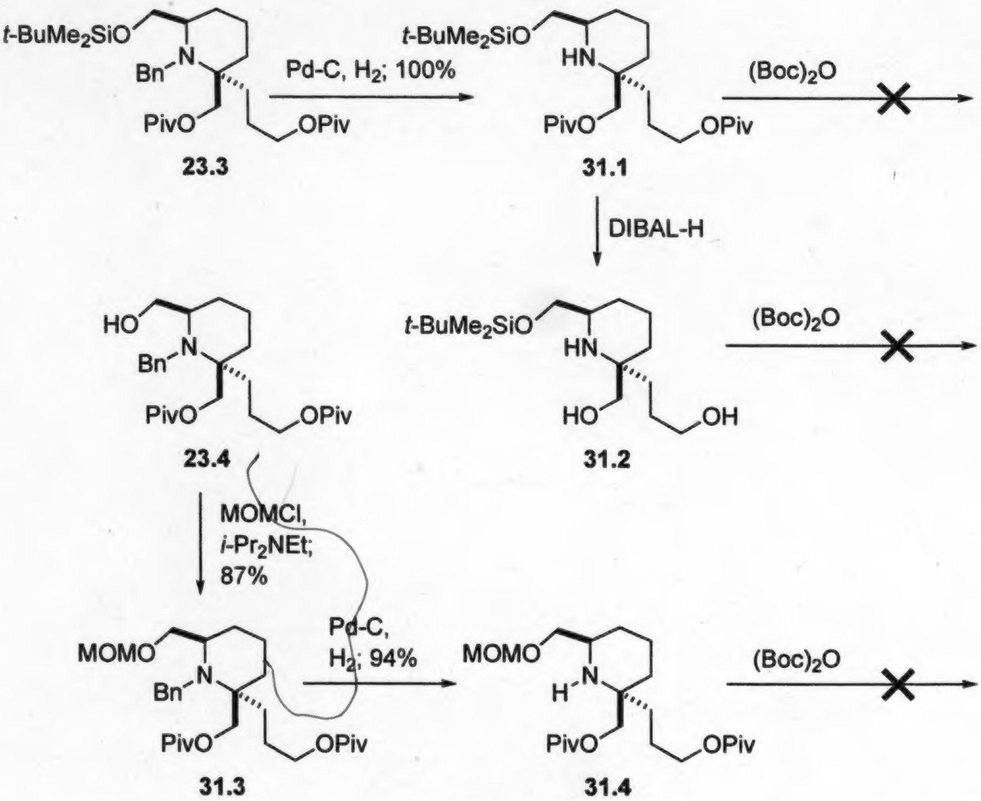
When we heated **29.1** in *N*-methylpiperidinone at reflux, the rearrangement occurred smoothly and the desired aldehyde **29.2** could be isolated in 95% yield after 4 h. The double bond was saturated by hydrogenation (65%) and the resulting aldehyde (**29.3**) was then homologated (KHMDS, $Ph_3PCH_2OCH_3$). Aldehyde **29.4** could be obtained in 78% yield after hydrolysis of the intermediate enol ethers. Oxidation of aldehyde **29.4** with *N*-iodosuccinimide (NIS) and K_2CO_3 in MeOH[39] gave ester **29.5** directly in 75% yield.

Our plan was to open the carbamate ring in the expectation that the resulting free amine would form a 6-membered lactam with the C(13) carbon chain. To our surprise, we met huge difficulties in attempts to open the 5-membered carbamate ring. As shown in Scheme 30, treatment of **29.5** with various bases in EtOH at reflux led only to acid **30.1**. Alcohol **30.2** was obtained from reduction of aldehyde **29.4**, but its carbamate ring also failed to open under various conditions: refluxing **30.2** with KOH or hydrazine in aqueous EtOH gave no reaction. $LiAlH_4$ reduction of **30.2** afforded a complex mixture. Treatment of an earlier intermediate, compound **23.6**, with either MeMgI or Me_3SiI also led to complete recovery of the starting material.



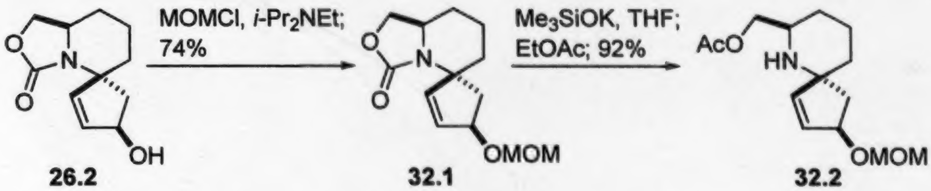
Scheme 30

We considered that if we used a different protecting group at an earlier stage we could avoid the difficulty of opening the carbamate. Accordingly, compound **23.3** was debenzylated by hydrogenolysis in quantitative yield to give amine **31.1** (Scheme 31). We failed to introduce a Boc group on the nitrogen, even in $ClCH_2CH_2Cl$ at reflux, probably due to steric hindrance of the nitrogen. To minimize the steric effect, we reduced both pivaloyl esters with DIBAL-H to release diol **31.2**, but even with this diol, we still could not put a Boc group on nitrogen. Later we thought that protection of alcohol **23.4** as its MOM ether (**23.4** → **31.3**, 87%), instead of the large TBS group, might lower the steric effect. However, after hydrogenolysis (**31.3** → **31.4**, 94%), amine **31.4** still resisted our attempts to block the nitrogen with a Boc group.



Scheme 31

Early this year (2004), an article published by Procopiou *et al.*[40] caught our attention. In this article, a convenient and efficient way to open 1,3-oxazolidin-2-ones by using potassium trimethylsilanolate in THF was described. To test if this method could be applied to our case, we made the MOM protected compound **32.1** from alcohol **26.2** (*i*-Pr_2NEt, MOMCl, 74%) (Scheme 32). Treatment of **32.1** with 2 equiv of Me_3SiOK in THF at reflux for 4 h, and then partitioning between EtOAc and water, gave the free amine **32.2** in excellent yield (92%).

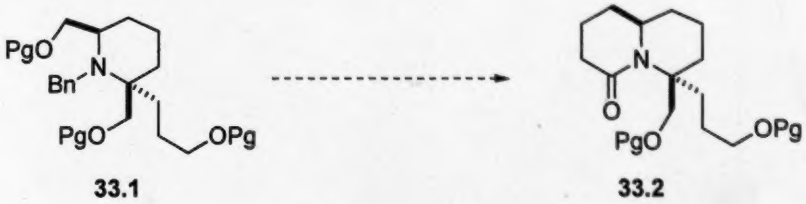


Scheme 32

Although we had a positive result from this test, we did not apply this method to compound **29.5**, because by this time we had already turned our attention to a modification of our synthetic route, as discussed in the following sections.

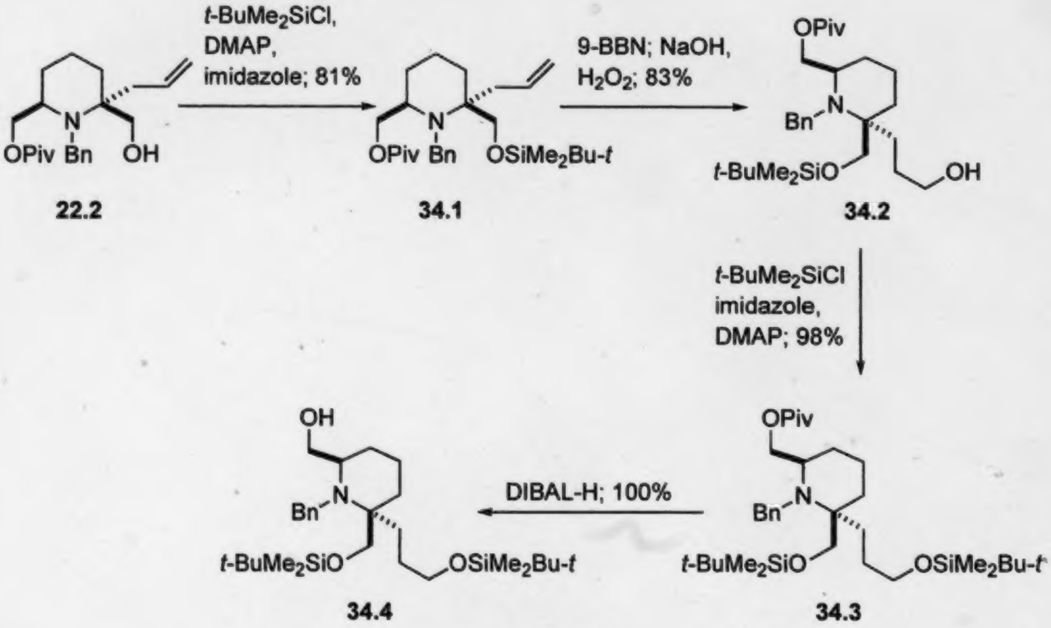
2.3 Studies related to construction of the left-hand 6-membered ring.

To avoid the difficulty of opening the 5-membered carbamate ring, we planned to aim for a bicyclic amide such as **33.2** (Scheme 33), in the hope that this approach would shorten our synthesis because the left-hand 6-membered amide ring of **33.2** was also part of the structure of halichlorine (in modified form).



Scheme 33

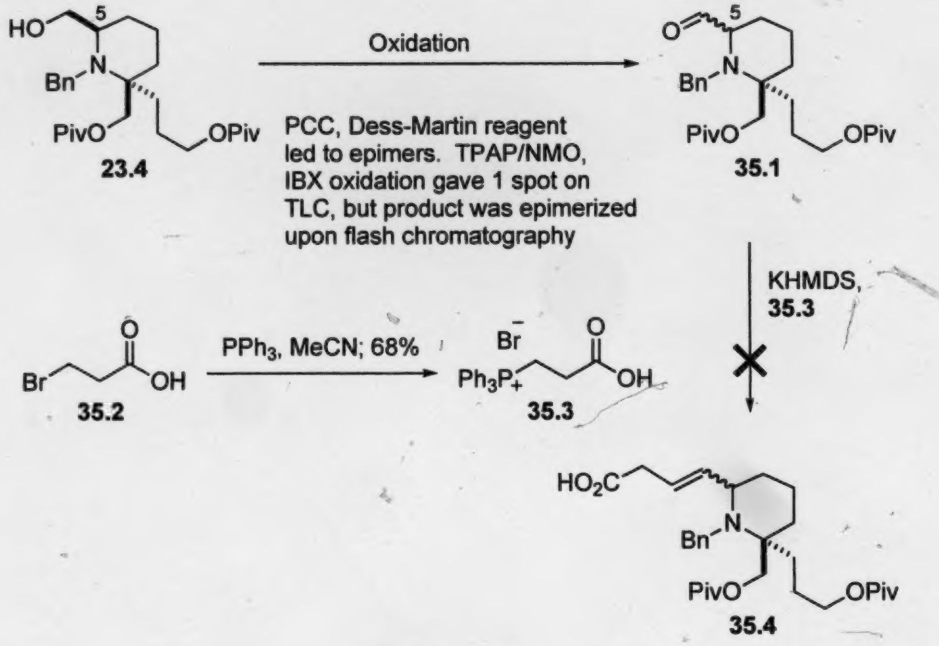
To obtain more starting material, we first converted the minor regioisomer **22.2** from the acylation of diol **22.1** into its TBS-protected silyl ether (Scheme 34). The silylation went well, but was extremely slow (48 h) and gave **34.1** in 81% yield. We suspected that the sterically hindered nature of the hydroxyl group retards ether formation with the large TBS group. It turned out that this assessment of the steric factors was very important in our later studies (see later sections).



Scheme 34

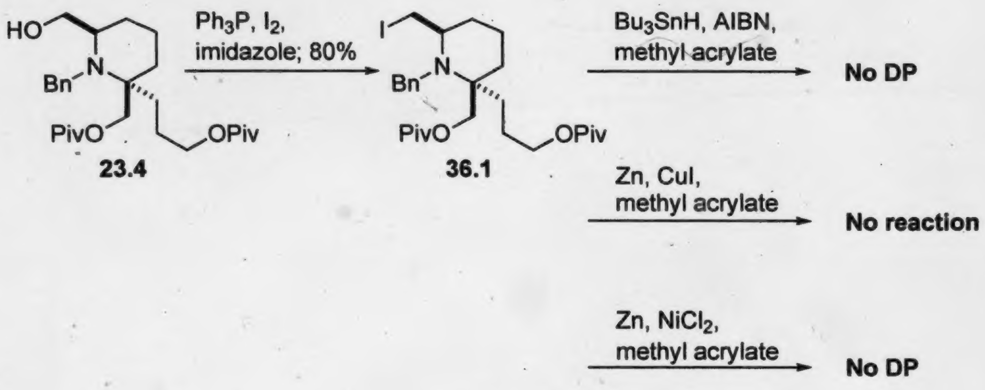
Hydroboration of **34.1** afforded the expected alcohol in 83% yield (Scheme 34). The free hydroxyl of **34.2** was then protected as its silyl ether to afford **34.3** (98%), and DIBAL-H reduction released a hydroxyl, and gave alcohol **34.4** quantitatively. This alcohol served as an alternative to alcohol **23.4** in some of our studies.

To build the C(5) carbon chain, we first started with alcohol **23.4**. This alcohol was oxidized, under various conditions (Scheme 35): PCC and Dess-Martin periodinane oxidations gave the C(5) epimer of **35.1** directly (two spots were observed on TLC plates); IBX and TPAP/NMO oxidations did give a single product spot on TLC; however, upon flash chromatographic purification, again a pair of C(5) epimers was obtained. We also tried to use the crude aldehyde directly in the next step without purification so as to avoid epimerization. Unfortunately, reaction of aldehyde **35.1** with Wittig reagent **35.3** (made from the bromoacid **35.2** by known procedures[41]) failed to give any of the desired product.


HO
5
Bn
N
PivO
OPiv
23.4
Oxidation
PCC, Dess-Martin reagent led to epimers. TPAP/NMO, IBX oxidation gave 1 spot on TLC, but product was epimerized upon flash chromatography
O
5
Bn
N
PivO
OPiv
35.1
KHMDS, 35.3
Br
O
OH
35.2
PPh3, MeCN; 68%
Br
Ph3P+
O
OH
35.3
HO2C
Bn
N
PivO
OPiv
35.4

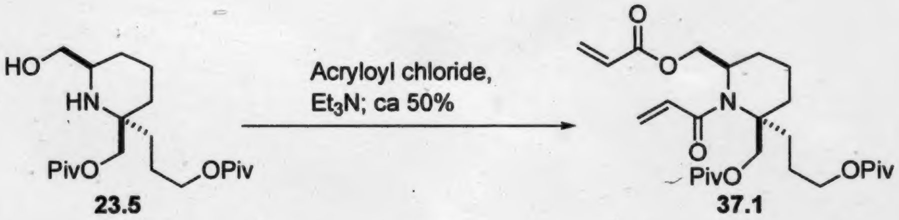
Scheme 35

Because the stereogenic center at C(5) in **35.1** is so sensitive, we converted the free hydroxyl of **23.4** to an iodide, as in **36.1** (Ph_3P, imidazole, I_2, 80%) (Scheme 36), and we planned to extend the C(5) carbon chain of **35.6** by radical coupling with methyl acrylate. However, the intermolecular coupling between the two components was unsuccessful either by the standard radical method (Bu_3SnH, AIBN) or by organometallic methods (Zn/CuI and $Zn/NiCl_2$[42]).



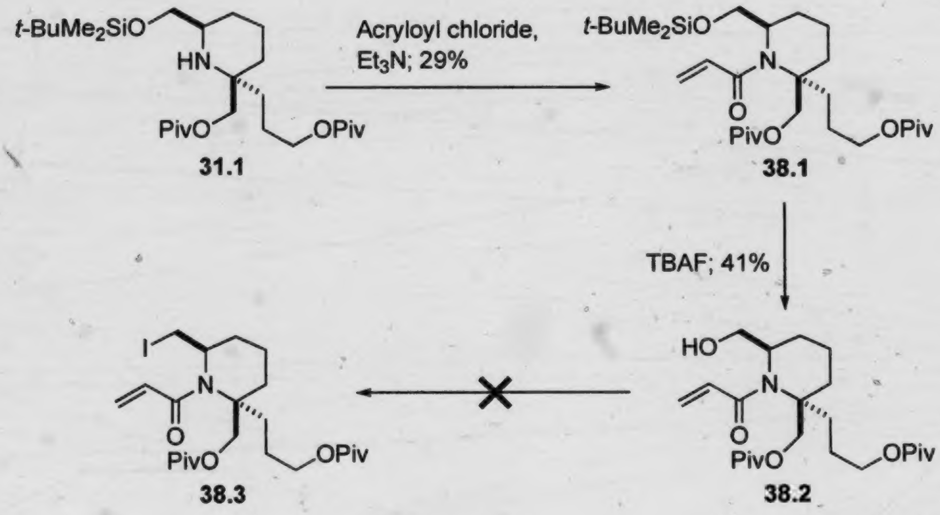
Scheme 36

We hoped that an intramolecular extension of the C(5) chain would be more successful. Accordingly, we treated alcohol **23.5** with 1 equiv of acryloyl chloride and excess Et_3N, hoping that the *N*-acylated product would predominate. However, we found that there was no selectivity between the hydroxyl and amine, and only the diacylated compound **37.1** (ca. 50%) could be obtained along with recovered starting material (Scheme 37).



Scheme 37

The lack of selectivity in the acylation forced us start with silylated amine **31.1** (Scheme 38). The amine nitrogen was acylated with acryloyl chloride to give amide **38.1** in 29% yield. The silyl protecting group was then removed by TBAF to give **38.2** (41%). Unfortunately, we could not make iodide **38.3** from alcohol **38.2**. If we had been able to generate **38.3**, we would have tried an intramolecular radical or organometallic process to join the iodine-bearing carbon to the terminus of the double bond.

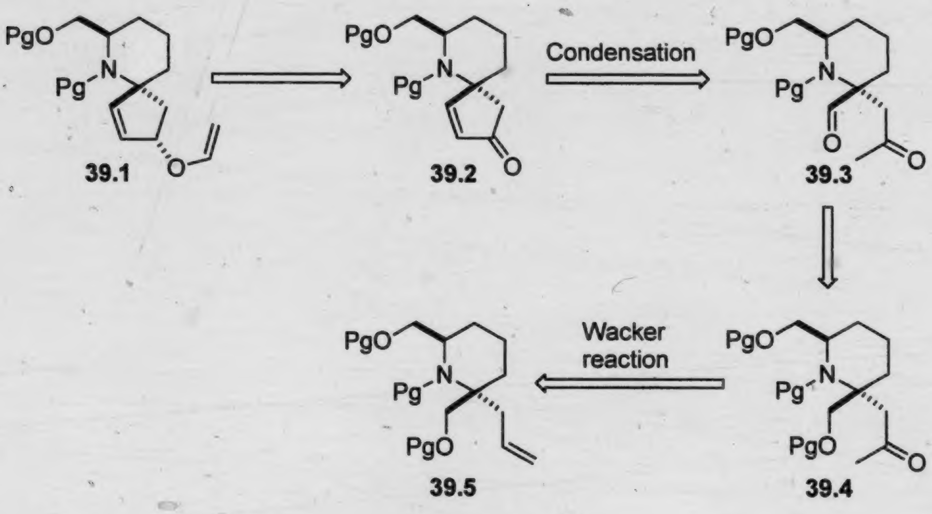


Scheme 38

The main lesson that we learnt from the above studies is that formation of the left-hand 6-membered ring of halichlorine was more challenging than expected at this stage, and so we decided to go back and build the azaspirocyclic core of halichlorine and pinnaic acid, but using a shorter and more efficient approach.

2.4 Studies to optimize the route towards the azaspirocylic core of halichlorine and pinnaic acid.

To shorten our previous approach towards the azaspiro core of halichlorine and pinnaic acid, we developed the retrosynthetic analysis shown in Scheme 39. The rearrangement precursor of type **39.1** would be made by stereoselective reduction of ketone **39.2**. This α,β-unsaturated cyclopentene would, in turn, be obtained from condensation of the aldehyde and ketone functionalities in **39.3**. We expected that ketone aldehyde **39.3** could be prepared from a compound of type **39.4** and, obviously, a Wacker reaction on compound **39.5** would lead to such a ketone.

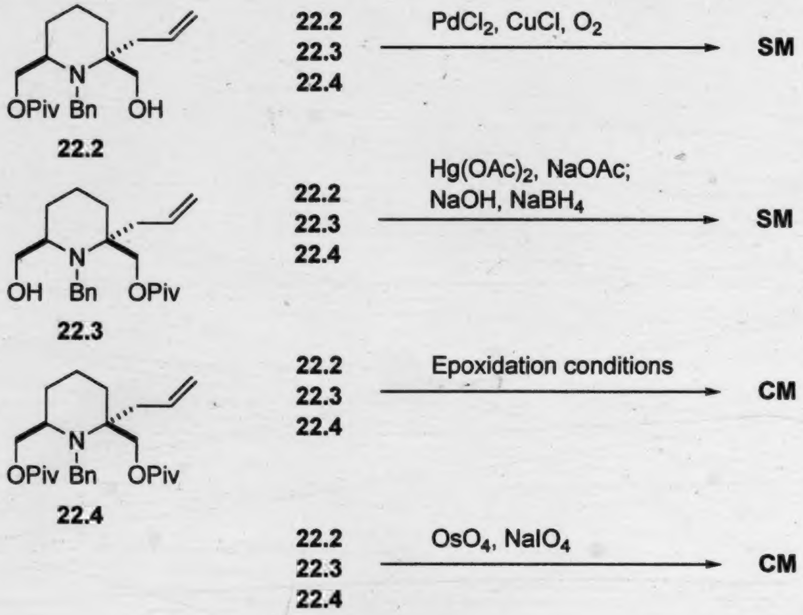


Scheme 39

If this plan were to work, the route would be much shorter than our previous approaches because a number of protection and de-protection steps are avoided. Examination of compounds we had already made in this project, suggested that alcohols **22.2** and **22.3**, and diester **22.4** (these three compounds are products obtained from the acylation of diol **22.1**, Scheme 22) are suitable starting materials to explore the new plan.

The results of these trials were very disappointing. Wacker oxidation of the terminal double bond of each of the three compounds, under standard conditions ($PdCl_2$, CuCl and

O_2 in DMF)[43] gave only recovered starting materials in (Scheme 40). Raising the reaction temperature to 55 °C and using a prolonged reaction time did not help. We assumed that the nitrogen is sufficiently basic to coordinate with the catalyst and thus reduce its reactivity. With this in mind, we repeated the above reactions with an excess of catalyst $PdCl_2$ (2 equiv), but we still did not obtain any trace of the desired products.

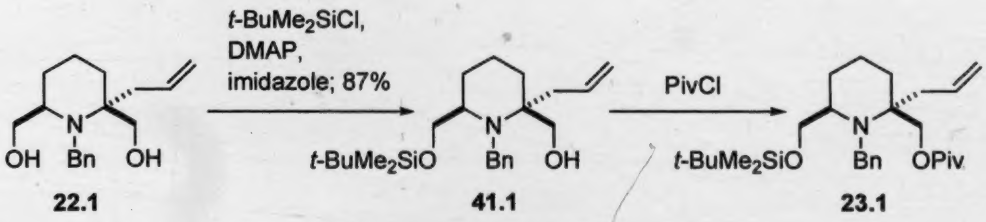


Scheme 40

Furthermore, to our surprise, the three compounds also failed to undergo oxymercuration.[44] Treatment of the compounds with $Hg(OAc)_2$, even in THF at reflux for a couple of days, followed by base and $NaBH_4$ workup, led to almost quantitative recovery of the starting materials.

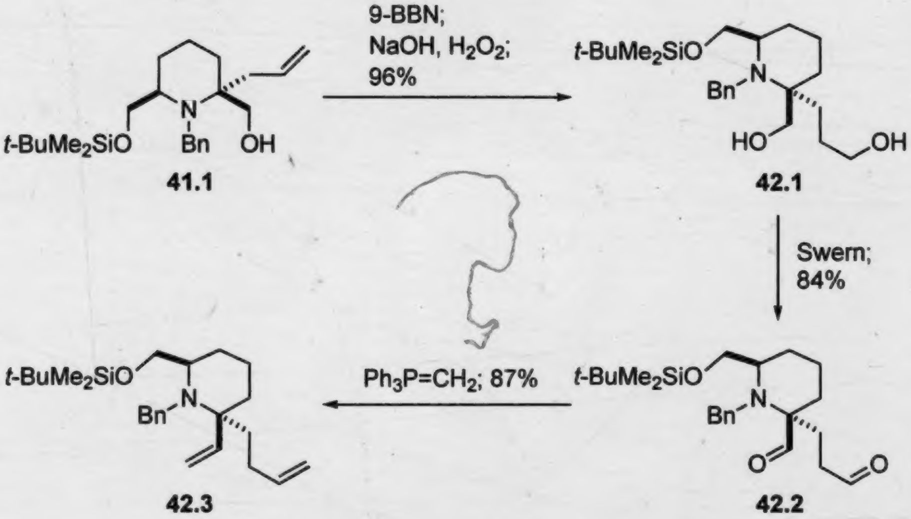
Epoxidation on the compounds, using mCPBA or $VO(acac)_2$-TBHP[45] furnished complex mixtures. Attempts to oxidatively cleave the terminal double bond under Lemieux-Johnson conditions[46] (OsO_4, $NaIO_4$) also failed. One possible reason for these results is that the nitrogen was also oxidized under our conditions to give the *N*-oxide. We did not try reductive workup, such as adding Ph_3P to the reaction mixture.

All the difficulties we encountered in the above studies forced us to abandon the synthetic plan in Scheme 39 and we now sought alternative ways to shorten our route. At this point, the observations we had made in the silylation of alcohol **22.2** (Scheme 34) were reconsidered: the silylation of the free hydroxyl in compound **22.2** required 48 hours to complete, but the silylation of alcohol **22.3** only took less than half an hour. Although we were not sure of the mechanistic reason, a steric effect certainly played a role here; and, more important, we thought that we might be able to use the rate difference of silylation of the two hydroxyls to selectively silylate the left-hand hydroxyl of diol **22.1**.



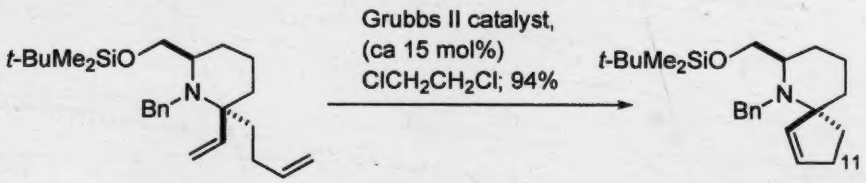
Scheme 41

Indeed, slow addition (ca. 30 min) of a CH_2Cl_2 solution of TBSCl (1.05 equiv) to a stirred and cooled (0 °C) mixture of diol **22.1**, imidazole and catalytic DMAP, gave mono-silylated compound **41.1** in 53% yield (Scheme 41). The identity of alcohol **41.1** was established by acylation with Me_3CCOCl – the ^1H and ^{13}C NMR spectra of the acylated product are identical to the spectra of compound **23.1**. Although the yield was not good at the beginning, we soon found that the yield could be improved dramatically (to ca. 75-80%) by quick addition of TBSCl at room temperature. The final optimized conditions for this selective silylation are: quick addition of 0.85 equiv of TBSCl to a CH_2Cl_2 solution of diol **22.1**, imidazole (1.8 equiv) and catalytic DMAP at room temperature. After 10 min, another portion of TBSCl (0.35 equiv) is added to the mixture. The reaction is complete in 30-60 min and the desired product can be isolated in 85-90% yield.



Scheme 42

With alcohol **41.1** in hand, we started our new approach to make the spiro ring. As shown in Scheme 42, hydroboration of the terminal double bond of **41.1** with more than 2 equiv of 9-BBN was successful, even without protecting the free hydroxyl. The intermediate alkylborane was then oxidized *in situ* with NaOH and H_2O_2 to afford diol **42.1** in 96% yield. Swern oxidation of both hydroxyls went smoothly to give dialdehyde **42.2** in high yield (83%). Double Wittig olefination of this dialdehyde, with KHMDS and excess Ph_3PCH_3Br, afforded diene **42.3** (87%).

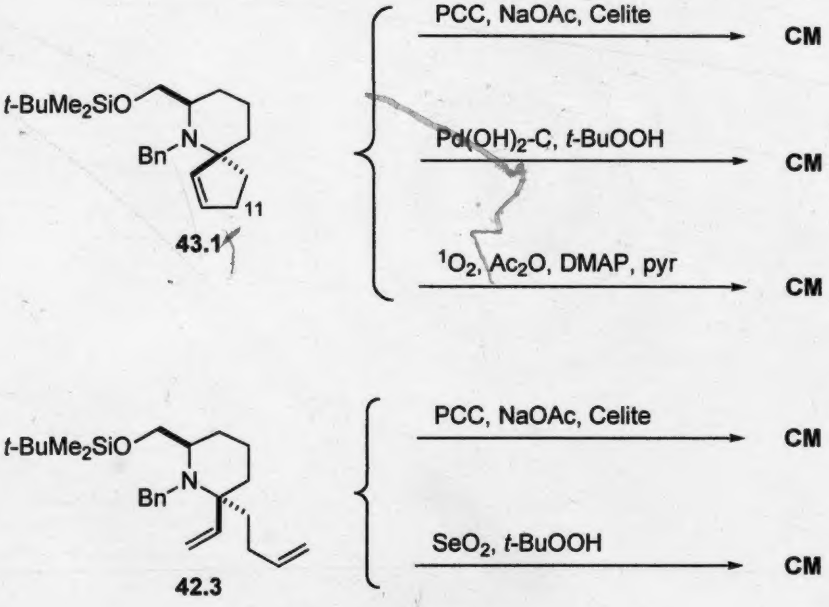


42.3 **43.1**

Scheme 43

Now the stage was set for the ring closing metathesis to generate the spiro ring. From the information we collected from our previous studies,[47] we realized that the benzylated amine nitrogen itself was quite basic. It might coordinate with the catalyst and reduce its reactivity. Therefore, we used the more powerful second generation Grubbs catalyst for the ring closure and found that with 5 mol% catalyst loading, the ring closing metathesis of diene **42.3** was extremely slow at room temperature and did not go to a completion. However, increasing the catalyst loading to ca. 15 mol%, and heating the reaction mixture at 50 °C, using $ClCH_2CH_2Cl$ as solvent, gave a clean reaction and the desired spirocyclic product **43.1** could be isolated in 93% yield (Scheme 43).

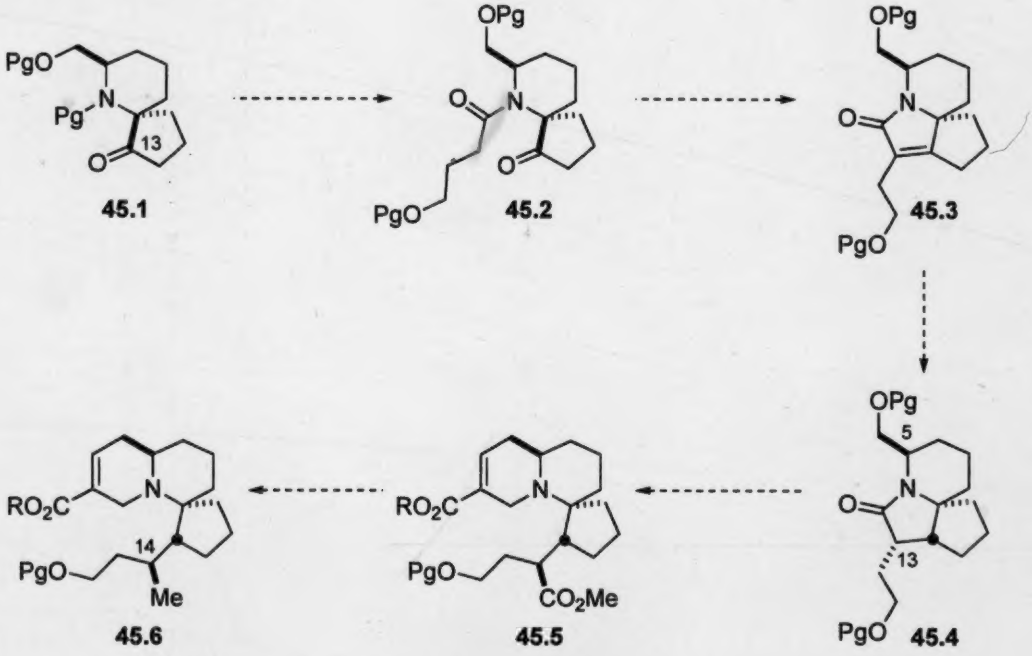
In this synthesis, we used only 10 steps to build up the spirobicyclic core of halichlorine and pinnaic acid from cheap and readily available 2,6-pyridinedicarboxylic acid (**19.1**). The next task was to do the allylic oxidation on the double bond of compound **43.1** and install the required functionalities at C(11) for the subsequent rearrangement. Unfortunately, again we were disappointed by unexpected difficulties.



Scheme 44

A number of allylic oxidation conditions were tried on compound **43.1** (Scheme 44): PCC oxidation, in the presence of AcONa and Celite, led to a complex mixture instead of the desired allylic oxidation product. Palladium(II)-mediated oxidations [($Pd(OH)_2$, t-BuOOH, K_2CO_3)][48] did not produce any of the desired product. The photooxygenation method reported by Mihelich *et al.*[49] also gave no trace of the desired product. We also did a few experiments on the compound before ring closing metathesis. PCC oxidation of diene **42.3** again led to a complex mixture. Selenium dioxide and t-BuOOH[34] oxidation, which worked on compound **23.9** in our very first synthesis, also produced a complex mixture, at either room temperature or in dioxane at reflux.

Although the above approach did not lead to an overlap with our first route, these studies showed us a new way to efficiently build the azaspiro core, and we were able to quickly make a spirobicyclic compound that corresponds to an advanced intermediate in Kibayashi's formal synthesis of halichlorine (**1**) and pinnaic acid (**2**).[19,20]

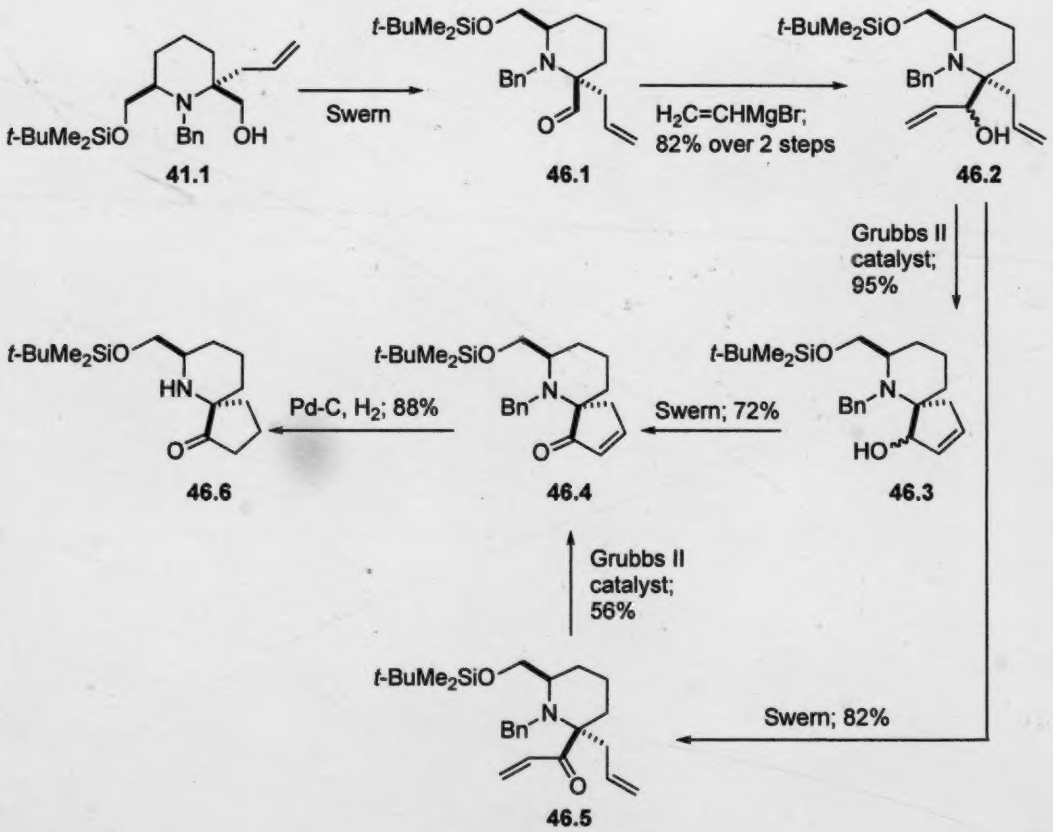


Scheme 45

2.5 Overlap with Kibayashi's formal synthesis of halichlorine and pinnaic acid.

Because we could not do the allylic oxidation on either compound **43.1** or diene **42.3**, we decided to abandon the original rearrangement route and develop a new plan to install the C(13) carbon chain. As shown in Scheme 45, this time we planned to make the spirocyclic compound **45.1** bearing a functional group at C(13). Removal of the nitrogen protecting group, followed by acylation with a suitable four-carbon unit would give amide **45.2**.

Intramolecular condensation of the amide side chain with the spiro ketone should afford tricyclic compound **45.3**. Hydrogenation of the double bond would be expected to deliver hydrogen on the convex face of the molecule, and thus generate the correct stereochemistry at C(13), as shown in **45.4**. Extension of the C(5) carbon chain, opening of the 5-membered amide ring and building up the left-hand 6-membered ring would bring us to a compound of type **45.5**. Finally, reduction of the C(14) ester group to a methyl group would set the required stereochemistry at C(14). A compound type **45.6** represents the core structure of halichlorine (**1**) with the correct stereochemistry at all four stereogenic centers.

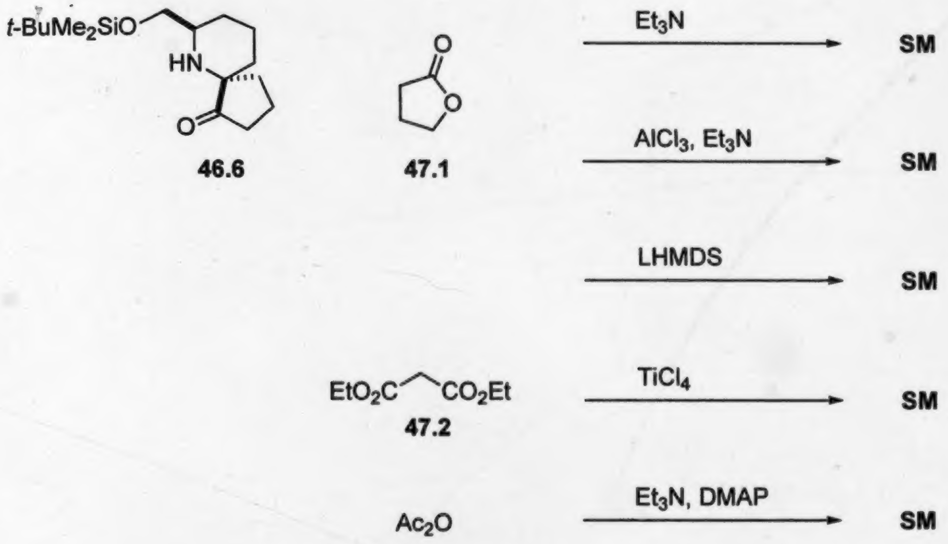


Scheme 46

To explore this new plan, we started with alcohol **41.1**. Either Swern or TPAP/NMO oxidation only gave about 60% of the desired aldehyde **46.1** after flash chromatographic purification (Scheme 46). On the assumption that **46.1** was unstable under the workup conditions, we decided to carry the crude aldehyde directly to next step without purification. Accordingly, the reaction mixture from the Swern oxidation was filtered through a short silica gel pad, concentrated and then treated with an excess of vinylmagnesium bromide to give alcohols **46.2** in 82% yield over two steps. Treatment of **46.2** with Grubbs II catalyst (ca. 5 mol% catalyst loading) in CH_2Cl_2 at reflux afforded spirobicyclic alcohol **46.3** in excellent yield (95%). Swern oxidation of this alcohol then produced ketone **46.4** (72%).

Alternatively, ketone **46.4** could also be obtained by first oxidation of alcohol **46.2** (**46.2** → **46.5**, Swern oxidation, 82%), followed by ring closing metathesis. However, ring closing metathesis of ketone **46.4** was extremely slow, even with more than 20 mol% catalyst loading and a higher reaction temperature, while the same reaction for alcohol **46.2** proceeded smoothly. A possible reason is that in compound **46.2**, the amine nitrogen could form an intramolecular hydrogen bond with the free hydroxyl, and thus reduce its ability to coordinate with the catalyst; hence the reaction could be carried out with a lower catalyst loading.

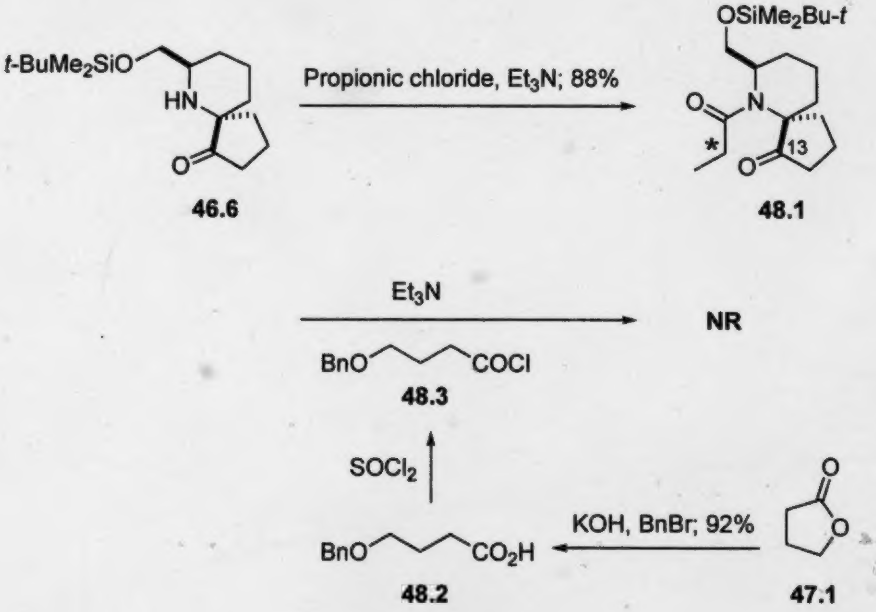
Hydrogenation of ketone **46.4** under standard conditions [(Pd-C, H_2 (35 psi))], served to saturate the double bond and also debenzylated the nitrogen, to gave amine **46.6** in high yield. This ketone amine is the key intermediate in our further studies.



Scheme 47

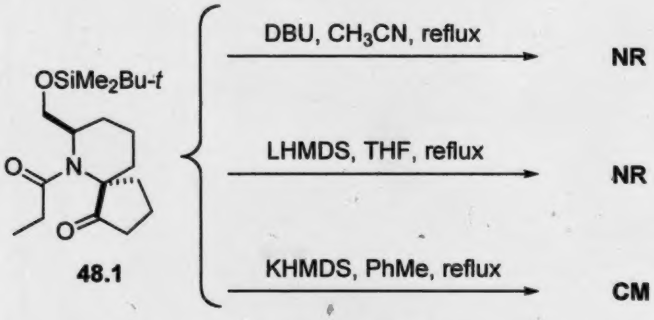
From amine **46.6**, we made a few attempts to attach a carbon chain to the nitrogen. However, treatment of **46.6** with γ-butyrolactone **47.1**, using Et_3N as base, led to complete recovery of the starting material (Scheme 47). Adding both substrates (1:1) to a mixture of $AlCl_3$ and Et_3N – this was claimed as an efficient method to activate the lactone[50] – also gave no reaction. Deprotonation of lactone **47.1** with LHMDS, followed by adding a limited amount of **46.6** (less than 0.5 equiv) again led to no reaction. In the last sequence, we hoped that the enolate would attack the ketone functionality on **46.6**, and the amine would then intramolecularly open the lactone ring to give us a tricyclic compound like **45.3** in one pot. Based on the same idea, we also tried the reaction between **46.6** and diethyl malonate (**47.2**), mediated by $TiCl_4$.[51] Unfortunately, again no reaction was observed. The lack of reactivity of this hindered secondary amine was also demonstrated by the following experiment: attempted acylation of the amine with Ac_2O also failed to give any product!

Later we found that treatment of amine **46.6** with more reactive species, such as EtCOCl in the presence of Et_3N as base, successfully gave the *N*-acylated product **48.1** in 88% yield (Scheme 48). Based on this observation, we made the corresponding four-carbon acid chloride **48.3** (made from γ-butyrolactone **47.1** by known procedures[52]) and tried the same acylation. However, treatment of amine **46.6** with freshly-prepared acid chloride **48.3** resulted no reaction. We attributed this result to steric effects.



Scheme 48

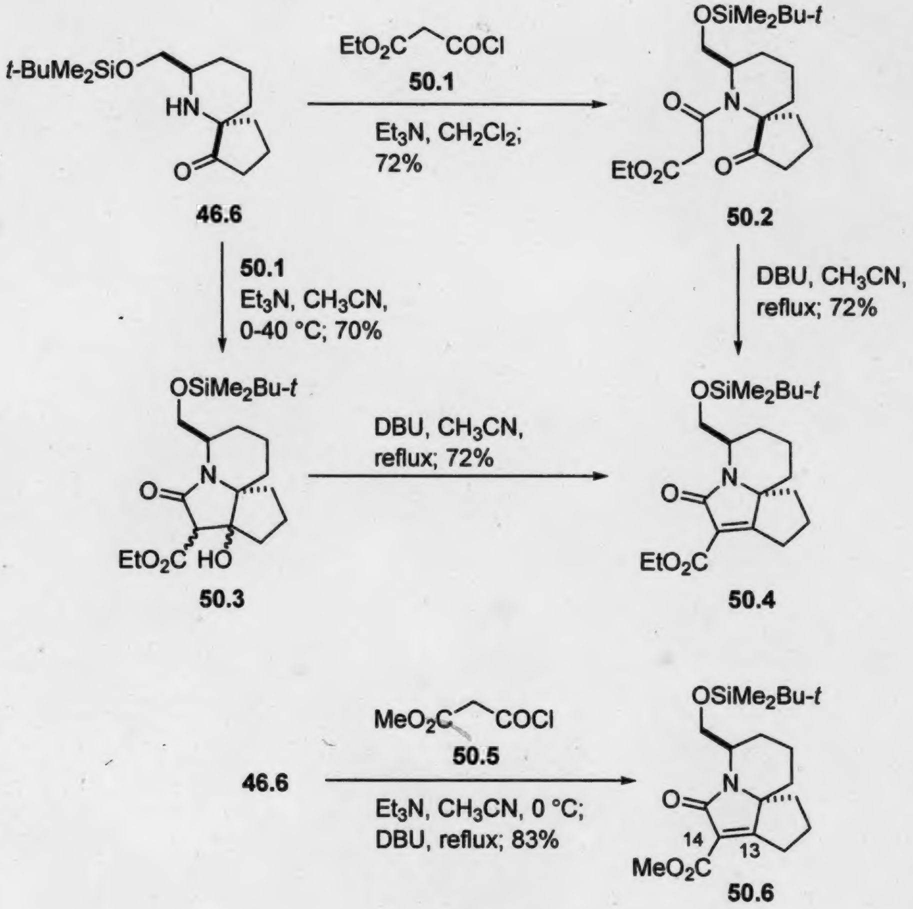
We considered preparing an acid chloride corresponding to **48.3**, but with a different protecting group on the terminal oxygen, but we first wanted to find out if the α carbon of the amide carbonyl (cf. **48.1**, starred atom) could close intramolecularly onto the C(13) ketone. Accordingly, amide **48.1** was treated with excess DBU in acetonitrile at reflux for 2 days, but no reaction occurred (Scheme 49). Repetition of this reaction with a stronger base, such as LHMDS in THF at reflux still produced no reaction and, when we treated **48.1** with KHMDS in PhMe at reflux for one week, only a complex mixture was obtained.



Scheme 49

The failure of the intramolecular condensation with amide **48.1** prompted us to increase the acidity of the proton near the amide carbonyl – the future C(14) in the structure of halichlorine. To this end, treatment of amine **46.6** with freshly distilled ethyl 3-chloro-3-oxomalonate (**50.1**) and Et_3N in CH_2Cl_2 at 0 °C gave the desired amide **50.2** in 72% yield (Scheme 50). In addition, if we used Acetonitrile as solvent in the reaction, and heated the mixture at 40 °C for 4 h after the addition of the acid chloride, we could isolate the tricyclic alcohol **50.3** in ca. 70% yield along with the elimination product **50.4** (ca. 29%). The relative stereochemistry of **50.3** was not established. Both amide **50.2** and alcohol **50.3** could be converted to compound **50.4** by treatment with DBU in Acetonitrile at reflux (72%).

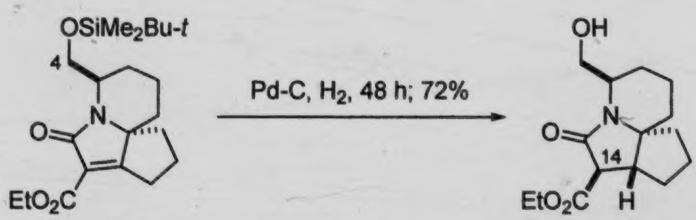
Based on these observations, a one-pot protocol to convert amine **46.6** to tricyclic ester **50.6** was developed: amine **46.6** was first treated with methyl 3-chloro-3-oxomalonate (from Aldrich) and Et_3N at 0 °C for 2 h, followed by addition of excess DBU and then the mixture was heated at reflux for 10 h to give **50.6** directly in excellent yield (83%).



Scheme 50

Now we moved on to the task of saturating the double bond between C(13) and C(14). From the shape of either **50.4** or **50.6**, we assumed that hydrogen would be delivered from the convex face of the structure and generate the desired stereochemistry at both C(13) and C(14).

To our surprise, the C(4) silyl ether was extremely sensitive to catalytic hydrogenation conditions. Hydrogenation of **50.6**, using 10% Pd-C catalyst and H_2 (40 psi) for 1 h led to a complete deprotection of the C(4) silyl ether. Repeating this reaction with lower H_2 pressures (as low as 15 psi), gave the same result. In addition, with short reaction times (2-12 h), we could see two product spots on TLC plates. However, when the reaction time was 48 hours, only one spot was seen on the TLC plate and we could isolate compound **51.1** in 72% yield (Scheme 51). The identity of **51.1** was established by extensive NMR studies, and is also based on the assumption that the C(14) stereogenic center in **51.1** is extremely sensitive, so that it underwent epimerization completely on prolonged reaction to give the most thermodynamically favored product shown in Scheme 51. Such an epimerization process also explains why we have two spots on the TLC plates after a short reaction time. All these assumptions were proven by our later work to overlap with Kibayashi's formal synthesis.

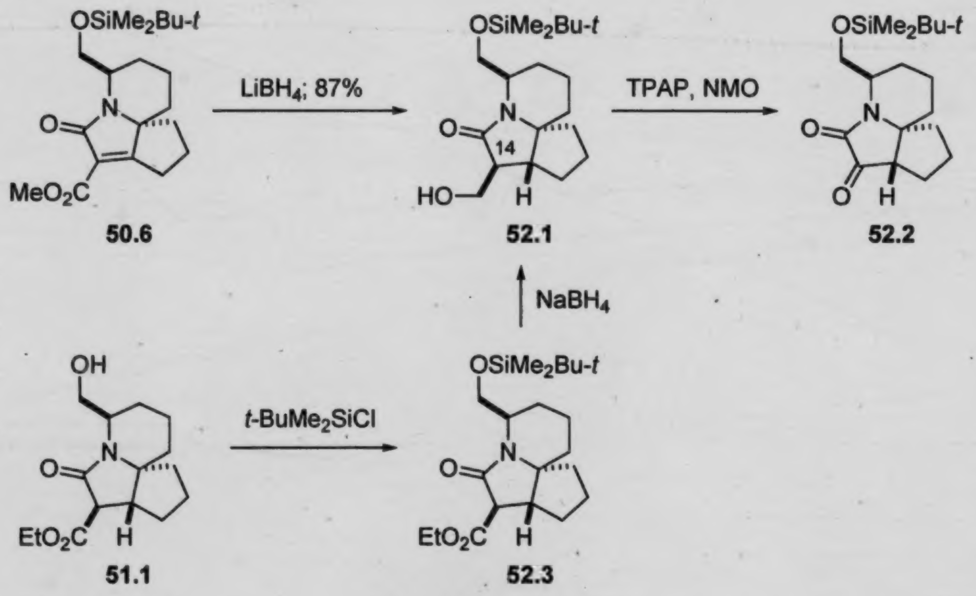


50.4 **51.1**

Scheme 51

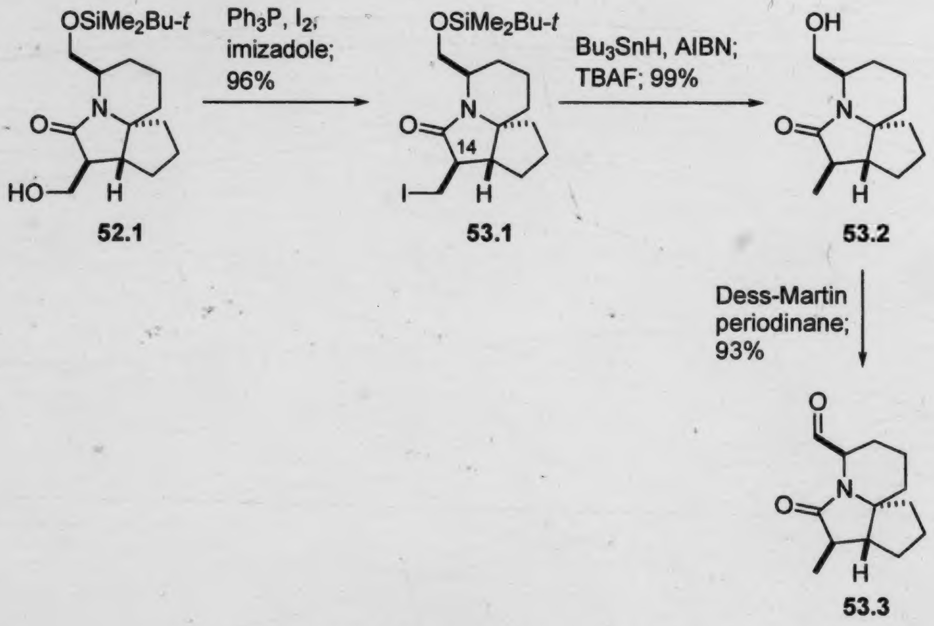
To reduce the sensitivity at C(14), we decided to reduce the ester group before the hydrogenation. Treatment of ester **50.6** with $LiBH_4$ in MeOH-THF gave cleanly one product in 87% yield (Scheme 52). This product proved to be alcohol **52.1** because conversion of alcohol **51.1** to its TBS ether (**51.1** → **52.3**) and reduction of the C(14) ester group with DIBAL-H gave the same compound.

At this point, we still wanted to oxidize the C(14) arm of alcohol **52.1**, homologate with a proper carbon chain and epimerize the C(14) stereogenic center to the α face, and follow our plan in Scheme 45. However, TPAP/NMO oxidation of alcohol **52.1** only led to the cleaved compound **52.2**.



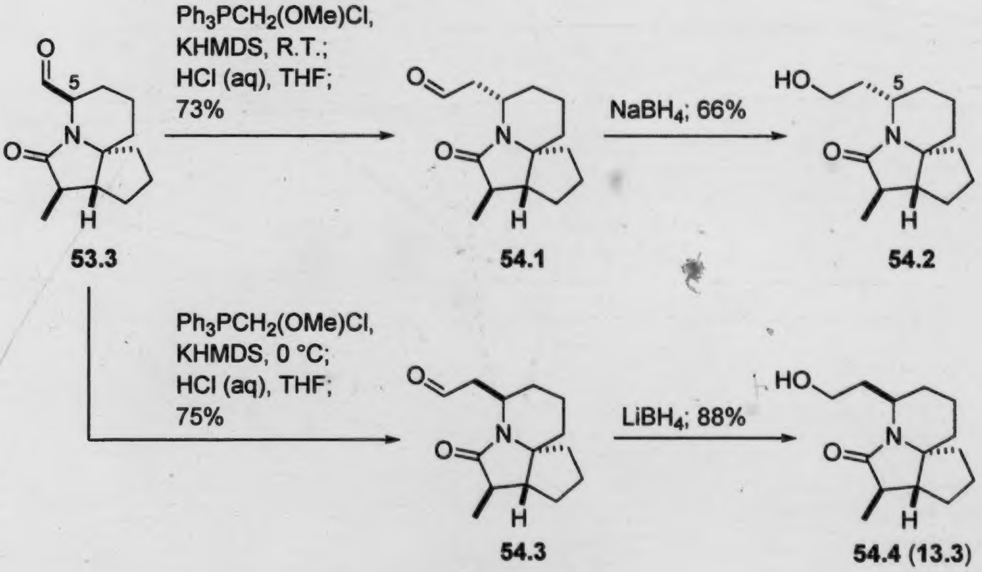
Scheme 52

We realized that from alcohol **52.1**, we could merge with Kibayashi's formal synthesis of halichlorine and pinnaic acid in a few steps. Doing this should be a valuable synthetic route because it only took 13 steps to reach alcohol **52.1** and the yields are good. With this in mind, we converted alcohol **52.1** to the corresponding iodide **53.1** in excellent yield (96%) (Scheme 53). Treatment of this iodide with excess Bu_3SnH and catalytic AIBN in PhH at reflux for 4 h, served as a radical reduction to release the C(14) methyl group. The crude product was then treated with excess TBAF for 10 h, diluted with Et_2O and filtered through a Celite pad to deprotect the silyl ether as well as to remove the alkyltin residues[53] from the product. After purification, alcohol **53.2** could be obtained in 99% yield. Dess-Martin oxidation of this alcohol afforded aldehyde **53.3** (93%).



Scheme 53

Very interesting results were obtained during the homologation of aldehyde **53.3**. First, we treated **53.3** with excess $Ph_3PCH_2(OMe)Cl$ and KHMDS (Scheme 54) at room temperature. The resulting vinyl ether was hydrolyzed with 1M hydrochloric acid-THF to give aldehyde **54.1** in 73% yield. Reduction of the aldehyde with $NaBH_4$ afforded alcohol **54.2** (66%). However, the ^1H and ^{13}C NMR spectra of our synthetic material (**54.2**) did not match the reported values for Kibayashi's compound **13.3**.[20] The obvious difference in the ^{1}H NMR spectrum is the chemical shift of the C(5) hydrogen, and so we assumed that **53.3** underwent epimerization at C(5). This result made us reconsider the conditions of the homologation of aldehyde **53.3**. Indeed, on repeating the homologation with exactly same conditions except that we added the aldehyde **53.3** to a *cooled* (0 °C) solution of the ylide, gave a different aldehyde (**54.3**) in 75% yield as the only product. Reduction of this aldehyde with $LiBH_4$ gave alcohol **54.4** in 88% yield. Alcohol **54.4** completely matched Kibayashi's report (compound **13.3**, Scheme 13). These studies showed that C(5) stereogenic center is very sensitive to base.



Scheme 54

At this point, our synthesis overlaps with Kibayashi's formal synthesis of halichlorine and pinnaic acid. Further studies are not necessary on this approach. We used only

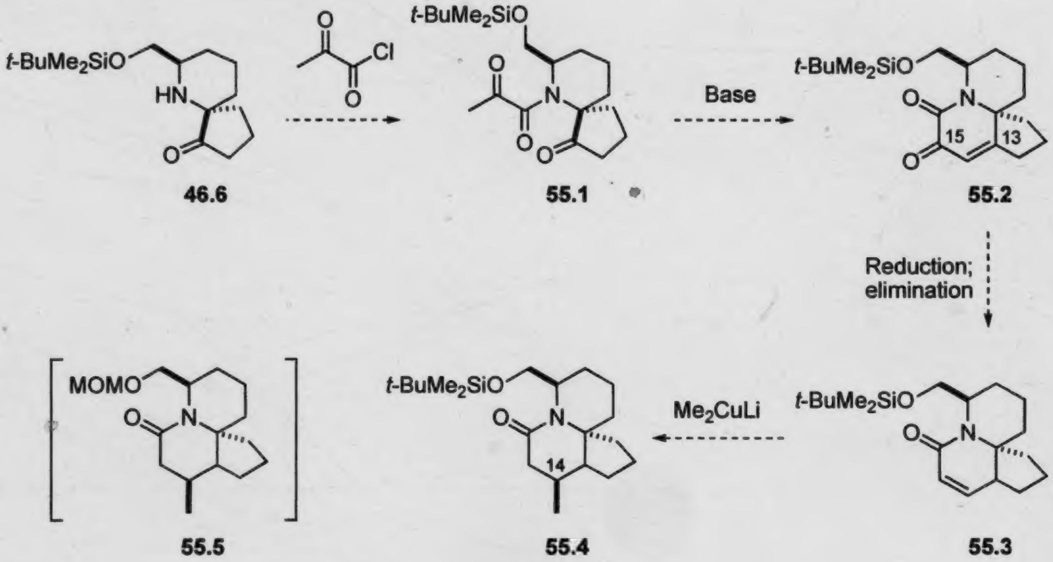
18 steps to obtain alcohol **54.4**; this is somewhat shorter (4 steps) than his reported route, and the overall yield is higher (0.6%).

2.6 Conclusion.

My approaches to the synthesis of halichlorine and pinnaic acid utilized Simpkins's methodology to generate the C(9) quaternary center at the beginning of the synthesis. However, we found that this methodology is probably only suitable for small scale reactions, in which a high ee% can be obtained. Applying this methodology on a large scale only led to products with an ee of 69%. More work needs to be done to solve this problem.

In our synthetic studies, we used ring closing metathesis to build the spiro five-membered ring. The second generation Grubbs catalyst served as a powerful olefin metathesis catalyst, even in the presence of a basic nitrogen (compound **42.3**).

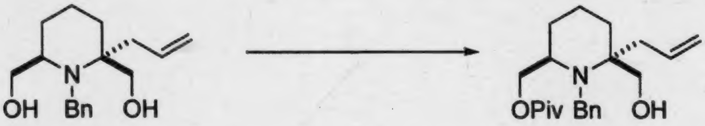
A Claisen rearrangement was used to install the C(13) side chain with the correct stereochemistry (**29.1** → **29.2**); and in later studies, we used nitrogen as an internal bridge to introduce the C(13) carbon chain (**46.6** → **50.6**). In the latter case, the route was taken to a point where it overlaps with Kibayashi's formal synthesis of halichlorine and pinnaic acid. However, further studies are in progress to elaborate one of our advanced intermediates in an independent way, so that the whole synthetic scheme is different from other routes being studied elsewhere. In particular, as shown in Scheme 55: from amine **46.6**, we plan to make amide **55.1**. This amide arm will be used to react with the C(13) carbonyl to produce tricyclic compound **55.2**. Enone reduction, followed by elimination of the resulting C(15) hydroxyl, will give unsaturated amide **55.3**. Introduction of the required C(14) methyl group will be done in the correct stereochemical sense by using Me_2CuLi, to give amide **55.4**. At this point, overlap with the other route reported in this laboratory (compound **55.5**),[29] should be straightforward, and the present route represents a shorter synthesis of **55.5**.



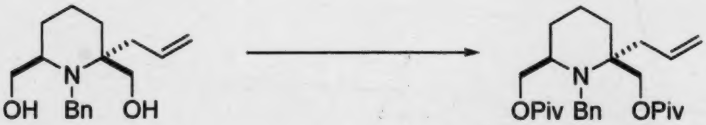
Scheme 55

III Experimental Section

[(2*R*,6*R*)-6-Allyl-1-benzyl-6-(hydroxymethyl)piperidin-2-yl]methyl Pivaloate (22.2) and [(2*R*,6*R*)-2-Allyl-1-benzyl-6-[(pivaloyloxy)methyl]piperidin-2-yl]methyl Pivaloate (22.4).



21.1 **22.2**



21.1 **22.4**

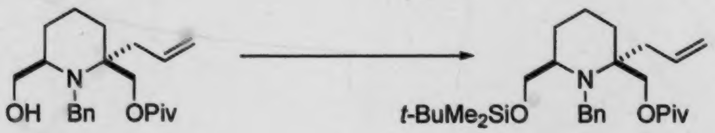
Me_3CCOCl (1.6 mL, 12.9 mmol) was added dropwise over ca. 45 min to a stirred and cooled (-20 °C) solution of diol **21.1** (3.33 g, 12.1 mmol), DMAP (30 mg) and *i*-Pr_2NEt (4.3 mL, 24.4 mmol) in CH_2Cl_2 (100 mL). After addition, the ice-bath was removed and stirring was continued for 5 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (100 mL), diluted with CH_2Cl_2 (100 mL), washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (4 x 25 cm), using 1:4 EtOAc-hexane, gave **22.3**[31] (3.25 g, 75%), **22.2** (0.50 g, 12%) and **22.4** (0.19 g, 4%), all as colorless oils.

Alcohol **22.2** had: FTIR (CH_2Cl_2 cast) 3525, 3063, 2936, 1727, 1636; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 9 H), 1.34-1.66 (m, 4 H), 1.71-1.86 (m, 2 H), 2.21-2.32 (m, 2 H), 2.59

(dd, J = 7.7, 13.8 Hz, 1 H), 2.97 (octet, J = 3.4 Hz, 1 H), 3.30 (d, J = 11.5 Hz, 1 H), 3.50-3.76 (m, 3 H), 4.14 (dd, J = 3.8, 11.2 Hz, 1 H), 4.20 (d, J = 17.2 Hz, 1 H), 5.04-5.16 (m, 2 H), 5.68-5.84 (m, 1 H), 7.19 (t, J = 7.2 Hz, 1 H), 7.30 (t, J = 7.6 Hz, 2 H), 7.38 (d, J = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.5 (t), 27.1 (q), 29.6 (t), 29.9 (t), 32.7 (t), 38.6 (s), 51.4 (t), 57.5 (d), 61.3 (s), 67.0 (t), 67.3 (t), 117.8 (t), 126.4 (d), 126.6 (d), 128.6 (d), 134.1 (d), 142.1 (s), 178.1 (s); exact mass *m/z* calcd for $C_{22}H_{33}NO_3$ 359.2460, found 359.2463.

Compound **22.4** had: FTIR (CH_2Cl_2 cast) 2973, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 9 H), 1.14 (s, 9 H), 1.38-1.74 (m, 6 H), 2.37-2.55 (m, 2 H), 2.92 (septet, J = 3.6 Hz, 1 H), 3.68 (dd, J = 7.6, 11.1 Hz, 1 H), 3.98 (s, 2 H), 4.00 (AB q, J = 17.0 Hz, $\Delta\nu_{AB}$ = 145.5 Hz, 2 H), 4.14 (dd, J = 3.5, 11.1 Hz, 1 H), 5.02-5.10 (m, 2 H), 5.64-5.84 (m, 1 H), 7.14 (t, J = 7.3 Hz, 1 H), 7.23 (t, J = 7.4 Hz, 2 H), 7.35 (d, J = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.9 (t), 27.09 (q), 27.11 (q), 28.8 (t), 31.0 (t), 34.7 (t), 38.6 (s), 38.8 (s), 51.6 (t), 56.4 (d), 58.9 (s), 65.5 (t), 69.7 (t), 117.9 (t), 126.2 (d), 126.7 (d), 128.1 (d), 134.1 (d), 142.1 (s), 178.1 (s); exact mass *m/z* calcd for $C_{27}H_{41}NO_4$ 443.3036, found 443.3031.

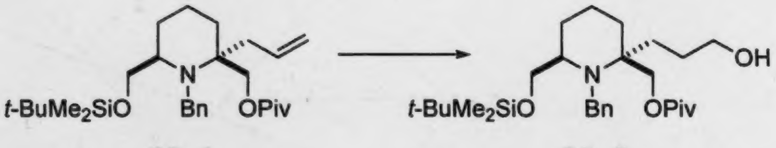
[(2*R*,6*R*)-2-Allyl-1-benzyl-6-[(*tert*-butyldimethylsilyloxy)methyl]piperidin-2-yl]methyl Pivaloate (23.1).



22.3 **23.1**

t-BuMe$_2$SiCl (2.10 g, 13.51 mmol) was added in one portion to a stirred and cooled (0 °C) solution of alcohol **22.3** (3.71 g, 10.35 mmol), imidazole (1.30 g, 19.10 mmol) and DMAP (30 mg) in CH_2Cl_2 (50 mL). Stirring was continued at 0 °C for 30 min. The ice bath was removed and stirring was continued at room temperature for 3 h and then the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (3.5 x 25 cm), using 1:19 EtOAc-hexane, gave **23.1** (4.58 g, 93%) as a colorless oil: FTIR ($CDCl_3$ cast) 3063, 2955, 1731, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ -0.12 (s, 3 H), -0.10 (s, 3 H), 0.78 (s, 9 H), 1.17 (s, 9 H), 1.37-1.66 (m, 5 H), 1.76-1.83 (m, 1 H), 2.43 (dd, *J* = 7.2, 14.2 Hz, 1 H), 2.53 (dd, *J* = 7.6, 14.2 Hz, 1 H), 2.81 (septet, *J* = 4.0 Hz, 1 H), 3.19 (dd, *J* = 8.1, 9.8 Hz, 1 H), 3.58 (dd, *J* = 3.7, 9.8 Hz, 1 H), 3.97 (s, 2 H), 3.98 (AB q, *J* = 16.9 Hz, $\Delta\nu_{AB}$ = 158.4 Hz, 2 H), 5.04-5.10 (m, 2 H), 5.77-5.86 (m, 1 H), 7.15 (t, *J* = 7.3 Hz, 1 H), 7.25 (t, *J* = 7.8 Hz, 2 H), 7.35 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.5 (s), 18.0 (t), 18.2 (s), 25.9 (q), 27.2 (q), 28.5 (t), 31.2 (t), 35.1 (t), 38.8 (s), 51.7 (t), 58.8 (s), 59.1 (d), 65.0 (t), 69.9 (t), 117.6 (t), 126.0 (d), 126.8 (d), 128.0 (d), 134.5 (d), 142.7 (s), 178.2 (s); exact mass *m/z* calcd for $C_{28}H_{47}NO_3Si$ 473.3325, found 473.3329.

[(2*R*,6*R*)-1-Benzyl-6-[(*tert*-butyldimethylsilyloxy)-methyl]-2-(3-hydroxypropyl)piperidin-2-yl]methyl Pivaloate (23.2).

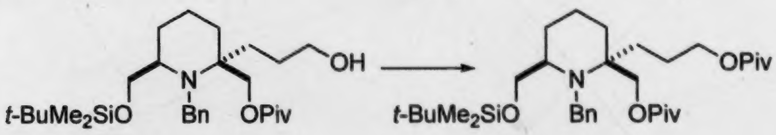


23.1 **23.2**

9-BBN (0.5 M, 46.0 mL, 23.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **23.1** (7.31 g, 15.45 mmol) in THF (60 mL). After addition, the ice-bath was removed and stirring was continued for 10 h. The mixture was cooled to 0 °C, and slowly quenched by addition of MeOH (20 mL), and then aqueous NaOH (2N, 50 mL) and H_2O_2 (30%, 12 mL) were added. The ice-bath was left in place but not recharged and stirring was continued for 2 h. The mixture was extracted with CH_2Cl_2 (3 x 60 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 1:9 to 1:4 EtOAc-hexane, gave alcohol **23.2** (7.29 g, 96%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3397, 3062, 2955, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.12 (s, 3 H), -0.09 (s, 3 H), 0.79 (s, 9 H), 1.16 (s, 9 H), 1.44 (s, 2 H), 1.52-1.83 (m, 9 H), 2.87 (septet, *J* = 4.1 Hz, 1 H), 3.25 (t, *J* = 9.4 Hz, 1 H), 3.57-3.65 (m, 3 H), 3.95 (AB q, *J* = 16.9 Hz, $\Delta\nu_{AB}$ = 126.7 Hz, 2 H), 3.97 (AB q, *J* = 11.5 Hz, $\Delta\nu_{AB}$ = 38.3 Hz, 2 H), 7.15 (t, *J* = 7.2 Hz, 1 H), 7.26 (t, *J* = 7.6 Hz, 2 H), 7.35 (d, *J* = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.5 (q), 18.1 (t), 18.2 (s), 25.9 (q), 27.0 (t), 27.2 (q), 27.6 (t), 30.5 (t), 38.8 (s), 50.9 (t), 58.5 (d), 58.6 (t), 63.5

(t), 64.7 (t), 69.9 (t), 126.1 (d), 126.8 (d), 128.0 (d), 142.6 (s), 178.2 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{50}NO_4Si$ (M + H), 492.3504, found 492.3506.

3-[(2*R*,6*R*)-1-Benzyl-6-[(*tert*-butyldimethylsilyloxy)-methyl]-2-[(pivaloyloxy)methyl]piperidin-2-yl]propyl Pivaloate (23.3).

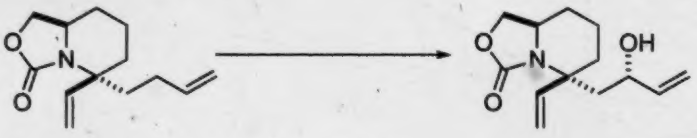


23.2 **23.3**

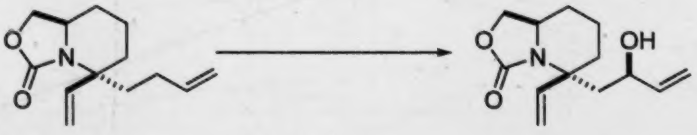
i-Pr_2NEt (6.0 mL, 34.4 mmol), followed by Me_3CCOCl (3.3 mL, 26.5 mmol) was added dropwise over ca. 5 min to a stirred and cooled (0 °C) solution of alcohol **23.2** (7.26 g, 14.8 mmol) and DMAP (20 mg) in CH_2Cl_2 (50 mL). The ice bath was removed and stirring was continued for 10 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 1:19 EtOAc-hexane, gave **23.3** (8.07 g, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3062, 2957, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.12 (s, 3 H), -0.10 (s, 3 H), 0.79 (s, 9 H), 1.17 (s, 9 H), 1.18 (s, 9 H), 1.42-1.83 (m, 10 H), 2.87 (septet, J = 3.8 Hz, 1 H), 3.27 (dd, J = 8.2, 9.8 Hz, 1 H), 3.60 (dd, J = 3.8, 9.9 Hz, 1 H), 3.94 (AB q, J = 17.1 Hz, $\Delta\nu_{AB}$ = 103.4 Hz, 2 H), 3.96 (AB q, J = 11.5 Hz, $\Delta\nu_{AB}$ = 28.4 Hz, 2 H), 4.03 (d, J = 2.1 Hz, 2 H), 7.16 (t, J = 7.3 Hz, 1 H), 7.26 (t, J = 7.8 Hz, 2 H), 7.34 (d, J = 7.4 Hz, 2 H); ^{13}C

NMR ($CDCl_3$, 125.7 MHz) δ -5.5 (q), 18.0 (t), 18.2 (s), 23.1 (t), 25.9 (q), 27.16 (q), 27.20 (q), 27.5 (t), 27.7 (t), 30.4 (t), 38.7 (s), 38.8 (s), 50.8 (t), 58.2 (d), 58.3 (s), 64.3 (t), 64.8 (t), 69.8 (t), 126.2 (d), 126.8 (d), 128.1 (d), 142.3 (s), 178.2 (s), 178.5 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{58}NO_5Si$ (M + H), 576.4079, found 576.4080.

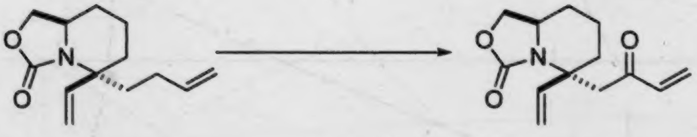
(5*R*,8a*R*)-Tetrahydro-5-[(*S*)-2-hydroxybut-3-enyl]-5-vinyl-1*H*-oxazolo[3,4-*a*]pyridine-3(5*H*)-one (25.2), (5*R*,8a*R*)-Tetrahydro-5-[(*R*)-2-hydroxybut-3-enyl]-5-vinyl-1*H*-oxazolo[3,4-*a*]pyridine-3(5*H*)-one (25.3) and (5*R*,8a*R*)-Tetrahydro-5-(2-oxobut-3-enyl)-5-vinyl-1*H*-oxazolo[3,4-*a*]pyridine-3(5*H*)-one (25.1).



23.9 **25.2**



23.9 **25.3**



23.9 **25.1**

t-BuOOH (5M, 5.2 mL. 26.0 mmol) was added dropwise over ca. 5 min to a stirred and cooled (0 °C) suspension of

SeO_2 (0.730 g, 6.58 mmol) in CH_2Cl_2 (40 mL). The ice bath was removed and stirring was continued for 30 min. A solution of diene **23.9** (2.430 g, 11.00 mmol) in CH_2Cl_2 (10 mL) was added dropwise over ca. 5 min and stirring was continued for 7 days at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using 1:9 to 1:3 *t*-BuOMe-CH_2Cl_2, gave alcohol **25.2** (yellow oil, 0.377 g, 18%), alcohol **25.3** (white solid, 0.837 g, 41%) and ketone **25.1** (yellow oil, 0.530 g, 26%). The yields are calculated after correction from recovered **23.9** (0.528 g, 2.39 mmol).

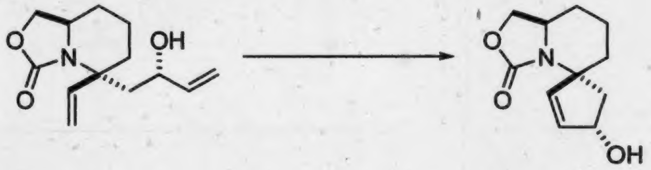
Alcohol **25.2** had: FTIR (CH_2Cl_2 cast) 3444, 3086, 2943, 1728, 1642 cm^{-1}; $[\alpha]_D = -6.44°$ (*c* 1.60, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22-1.33 (m, 1 H), 1.46-1.66 (m, 3 H), 1.74-1.82 (m, 1 H), 1.88-2.06 (m, 3 H), 3.30 (s, 1 H), 3.65-3.74 (m, 1 H), 3.80 (dd, *J* = 8.0, 10.7 Hz, 1 H), 4.08-4.14 (m, 1 H), 4.43 (dd, *J* = 7.4, 7.9 Hz, 1 H), 5.08 (td, *J* = 1.4, 10.4 Hz, 1 H), 5.19-5.32 (m, 3 H), 5.88 (ddd, *J* = 5.6, 10.5, 17.2 Hz, 1 H), 6.28 (ddd, *J* = 0.7, 11.1, 17.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.1 (t), 29.0 (t), 38.0 (t), 38.5 (t), 53.2 (d), 58.6 (s), 68.6 (t), 68.8 (d), 113.3 (t), 114.5 (t), 140.2 (d), 141.8 (d), 158.1 (s); exact mass *m/z* calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1361.

Alcohol **25.3** had: FTIR (CH_2Cl_2 cast) 3359, 3074, 2938, 1717, 1640 cm^{-1}; $[\alpha]_D = +1.33°$ (*c* 0.30, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (dq, *J* = 4.2, 11.0 Hz, 1 H), 1.41 (dtd, *J* = 1.3, 2.9, 12.8 Hz, 1 H), 1.49-1.75 (m, 4 H), 1.83-1.88 (m, 1 H), 1.97 (s, 1 H), 2.17 (ddd, *J* = 1.4, 9.2, 15.4 Hz, 1 H), 3.69 (dd, *J* = 8.0, 10.6 Hz, 1 H), 3.93-4.00 (m, 1 H), 4.33 (t, *J* = 7.9 Hz, 1 H), 4.67-4.72 (m, 1 H), 4.96 (d, *J* = 17.8 Hz, 1 H), 5.01 (td, *J* = 1.4, 10.4 Hz, 1

H), 5.15 (d, *J* = 11.2 Hz, 1 H), 5.19 (td, *J* = 1.5, 17.1 Hz, 1 H), 5.85 (ddd, *J* = 6.0, 11.2, 17.2 Hz, 1 H), 6.39 (ddd, *J* = 1.3, 11.1, 17.6 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 19.4 (t), 29.4 (t), 37.3 (t), 38.2 (t), 52.7 (d), 59.2 (s), 68.5 (t), 69.4 (d), 111.2 (t), 113.4 (t), 141.7 (d), 142.5 (d), 158.0 (s); exact mass *m/z* calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1366.

Ketone **25.1** had: FTIR (CH_2Cl_2 cast) 3089, 2944, 1747, 1687, 1611 cm^{-1}; $[\alpha]_D$ = -3.26° (*c* 1.90, CH_2Cl_2); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.33-1.44 (m, 1 H), 1.54-1.82 (m, 3 H), 1.87-1.94 (m, 1 H), 2.10-2.18 (m, 1 H), 3.13 (AB q, *J* = 15.0 Hz, $\Delta\nu_{AB}$ = 145.1 Hz, 2 H), 3.76 (dd, *J* = 8.2, 9.9 Hz, 1 H), 4.01-4.10 (m, 1 H), 4.38 (t, *J* = 8.0 Hz, 1 H), 5.15 (d, *J* = 17.5 Hz, 1 H), 5.19 (d, *J* = 10.9 Hz, 1 H), 5.77 (dd, *J* = 1.1, 10.5 Hz, 1 H), 6.17-6.40 (m, 3 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 17.5 (t), 27.9 (t), 32.3 (t), 42.9 (t), 52.6 (d), 58.4 (s), 68.6 (t), 113.6 (t), 128.6 (t), 137.2 (d), 139.8 (d), 156.4 (s), 198.1 (s); exact mass *m/z* calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1203.

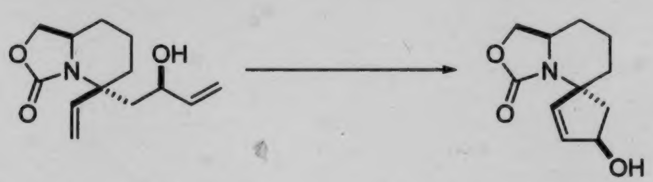
(5'*R*,8'a*R*)-Tetrahydrospiro[(*S*)-4-hydroxycyclopent-2-ene-1,5'(1'H)oxazolo[3,4-*a*]pyridine]-3'-one (26.1).



25.2 **26.1**

Grubbs II catalyst (**23.11**) (5 mg) was added to a stirred solution of **25.2** (100 mg, 0.42 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 3 h and the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using EtOAc, gave **26.1** (82 mg, 93%) as a colorless oil: FTIR ($CDCl_3$ cast) 3401, 2936, 1742, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24-1.43 (m, 2 H), 1.48-1.69 (m, 2 H), 1.78-1.96 (m, 3 H), 2.31 (dd, *J* = 7.0, 14.2 Hz, 1 H), 2.86 (s, 1 H), 3.62-3.71 (m, 1 H), 3.75 (dd, *J* = 7.9, 10.6 Hz, 1 H), 4.34 (t, *J* = 7.5 Hz, 1 H), 4.68 (td, *J* = 2.3, 6.9 Hz, 1 H), 5.92 (d, 5.5 Hz, 1 H), 5.99 (dd, *J* = 2.3, 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.3 (t), 28.6 (t), 37.2 (t), 44.2 (t), 55.0 (d), 66.0 (s), 68.0 (t), 133.7 (d), 137.9 (d), 157.5 (s); exact mass *m/z* calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1051.

5'*R*,8'a*R*)-Tetrahydrospiro[(*R*)-4-hydroxycyclopent-2-ene-1,5'(1'H)oxazolo[3,4-*a*]pyridine]-3'-one (26.2).

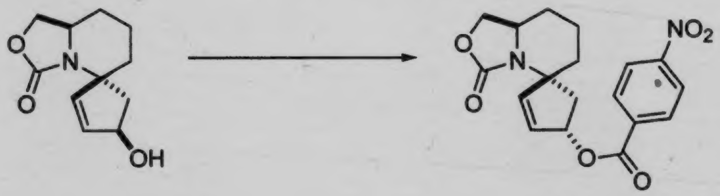


25.3 **26.2**

Grubbs II catalyst (**23.11**) (15 mg) was added to a stirred solution of **25.3** (0.689 g, 2.91 mmol) in CH_2Cl_2 (40 mL). The resulting mixture was stirred for 3 h and the solvent was concentrated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using EtOAc, gave **26.2** (0.570 g, 94%) as a colorless oil: FTIR ($CDCl_3$ cast) 3401, 2936, 1742, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24-1.38 (m, 1 H), 1.56-1.72 (m, 4 H), 1.84-1.92 (m, 2 H), 2.03 (dd, *J* = 1.8, 13.8 Hz, 1 H), 2.12-2.18 (m, 1 H), 3.61-3.70 (m, 1 H), 3.78 (dd, *J* = 8.2, 9.0 Hz, 1 H), 4.33 (dd, *J* =

7.6, 8.2 Hz, 1 H), 4.97-5.01 (m, 1 H), 5.90 (dd, *J* = 2.3, 5.6 Hz, 1 H), 6.24 (d, *J* = 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.6 (t), 29.5 (t), 38.0 (t), 42.8 (t), 54.6 (d), 67.7 (s), 67.8 (t), 131.5 (d), 140.1 (d), 155.9 (s); exact mass *m/z* calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1050.

(5'*R*,8'a*R*)-Tetrahydrospiro[(*S*)-4-(4-nitrobenzoyloxy)-cyclopent-2-ene-1,5'(1'*H*)oxazolo[3,4-*a*]pyridine]-3'-one (27.1).

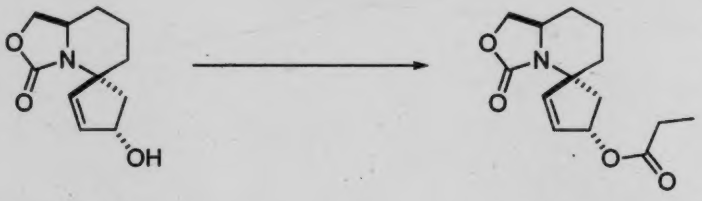


26.2 **27.1**

DEAD (0.42 mL, 2.53 mmol) was added dropwise to a stirred and cooled (0 °C) solution of Ph_3P (0.710 g, 2.73 mmol), 4-nitrobenzoic acid (0.350 g, 2.10 mmol) and alcohol **26.2** (0.190 g, 0.909 mmol) in PhH (20 mL). The cold bath was removed and the mixture was stirred for 10 h. EtOAc (50 mL) was added and the mixture was washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:4 EtOAc-hexane, gave **27.1** (0.290 g, 89%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3110, 2940, 1752, 1720, 1607 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24-1.40 (m, 2 H), 1.58-1.70 (m, 2 H), 1.88-1.98 (m, 3 H), 2.86 (dd, *J* = 7.3, 13.3 Hz, 1 H), 3.58-3.68 (m, 1 H), 3.80 (dt, *J* = 0.7, 9.2 Hz, 1 H), 4.36 (t, *J* = 8.0 Hz, 1 H), 5.84-5.89 (m, 1 H), 5.96 (ddd, *J* = 0.9, 1.9, 7.6 Hz, 1 H), 6.44 (td,

J = 0.9, 5.7 Hz, 1 H), 8.16-8.26 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.8 (t), 29.3 (t), 36.2 (t), 40.2 (t), 54.3 (d), 65.9 (s), 68.0 (t), 78.7 (d), 123.4 (d), 127.2 (d), 130.8 (d), 135.4 (s), 141.8 (d), 150.5 (s), 156.1 (s), 164.6 (s); exact mass m/z calcd for $C_{18}H_{18}N_2O_6$ 358.1165, found 358.1154.

(5'*R*,8'a*R*)-Tetrahydrospiro[(*S*)-4-propionyloxy)cyclopent-2-ene-1,5'(1'*H*)oxazolo[3,4-*a*]pyridine]-3'-one (28.1).

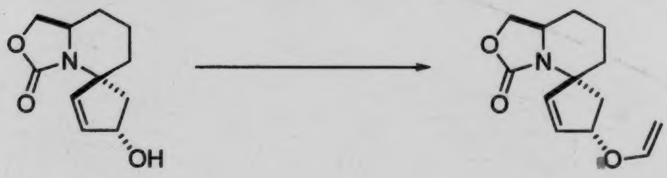


26.1 **28.1**

EtCOCl (15 μL, 0.17 mmol) was added dropwise over ca. 1 min to a stirred and cooled (0 °C) solution of alcohol **26.1** (9.0 mg, 0.04 mmol), i-Pr_2NEt (40 μL, 0.22 mmol) and DMAP (3 mg) in CH_2Cl_2 (3 mL). The ice bath was removed and stirring was continued for 3 h. The reaction mixture was then quenched by addition of saturated aqueous NH_4Cl (3 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave **28.1** (10.0 mg, 88%) as a colorless oil: FTIR ($CDCl_3$ cast) 2939, 1752, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, J = 7.6 Hz, 3 H), 1.25-1.36 (m, 2 H), 1.49-1.68 (m, 2 H), 1.74 (ddd, J = 1.2, 5.8, 17.6 Hz, 1 H), 1.84-1.94 (m, 2 H), 2.30 (dq, J = 1.0, 7.6 Hz, 2 H), 2.76 (dd, J = 7.3, 13.1 Hz, 1

H), 3.57-3.65 (m, 1 H), 3.78 (dd, *J* = 8.3, 9.2 Hz, 1 H), 4.34 (dd, *J* = 7.7, 8.2 Hz, 1 H), 5.55-5.61 (m, 1 H), 5.84 (dd, *J* = 1.9, 5.7 Hz, 1 H), 6.34 (dd, *J* = 1.5, 5.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 9.0 (q), 20.8 (t), 27.6 (t), 29.4 (t), 36.0 (t), 40.3 (t), 54.3 (d), 65.8 (s), 67.9 (t), 76.9 (d), 127.9 (d), 140.6 (d), 156.0 (s), 174.5 (s); exact mass *m/z* calcd for $C_{14}H_{19}NO_4$ 265.1314, found 265.1348.

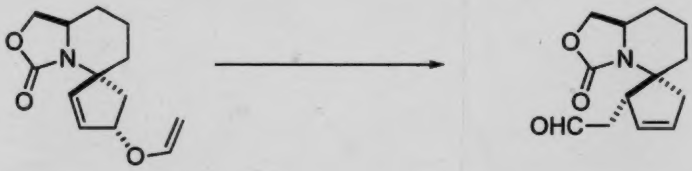
(5'*R*,8'a*R*)-Tetrahydrospiro[(*S*)-4-vinyloxy]cyclopent-2-ene-1,5'(1'*H*)oxazolo[3,4-*a*]pyridine]-3'-one (29.1).



26.1 **29.1**

Hg(OAc)$_2$ (48.0 mg, 0.15 mmol) and AcONa (25.0 mg, 0.31 mmol) were added in one portion to a stirred solution of **26.1** (24.2 mg, 0.12 mmol) in butyl vinyl ether (3 mL). The resulting mixture was heated at reflux for 3 days and cooled to room temperature. K_2CO_3 (30 mg) was added and the mixture was filtered through a Celite pad (1.5 x 1 cm). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave **29.1** (25.9 mg, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2936, 1752, 1617 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 0.51-0.62 (m, 1 H), 0.67-0.72 (m, 1 H), 0.84-0.94 (m, 2 H), 1.07-1.22 (m, 2 H), 1.73 (ddd, *J* = 1.7, 5.8, 17.2 Hz, 1 H), 2.15 (dd, *J* = 7.2, 13.0 Hz, 1 H), 2.58-2.66 (m, 1 H), 3.06 (t, *J* = 8.2 Hz, 1 H), 3.52 (t, *J* = 7.8 Hz, 1 H), 4.07 (dd, *J* = 1.6, 6.7 Hz, 1 H), 4.36 (dd, *J* = 1.6, 14.3 Hz, 1 H), 4.61-4.66 (m, 1 H), 5.77 (dd, *J* = 1.8, 5.7 Hz, 1 H), 6.40 (dd, *J* = 1.5, 5.8 Hz, 1 H), 6.49 (ddd, *J* = 0.4, 6.7, 20.4 Hz, 1 H); ^{13}C NMR (C_6D_6, 125.7 MHz) δ 21.1 (t), 29.1 (t), 36.1 (t), 40.5 (t), 53.7 (d), 65.8 (s), 67.4 (t), 80.9 (d), 88.5 (t), 128.3 (d), 141.0 (d), 150.5 (d), 155.6 (s); exact mass *m/z* calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1209.

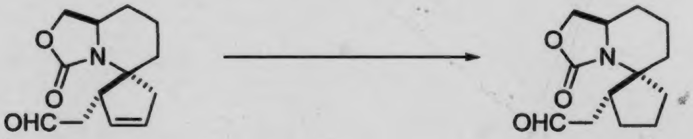
(5'*R*,8'a*R*)-Tetrahydrospiro[(*R*)-2-(2-oxoethyl)cyclopent-3-ene-1,5'(1'*H*)oxazolo[3,4-*a*]pyridine]-3'-one (29.2).



29.1 **29.2**

A solution of **29.1** (72.4 mg, 0.31 mmol) in NMP (0.8 mL) was heated at reflux (205 °C) for 4 h, and then cooled to room temperature. Flash chromatography of the mixture over silica gel (the whole mixture was applied directly to the top of the column) (1 x 20 cm), by using 1:3 EtOAc-hexane, gave aldehyde **29.2** (68.8 mg, 95%) as a colorless oil: FTIR ($CDCl_3$ cast) 2940, 2810, 2720, 1743, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42-1.51 (m, 1 H), 1.61-1.71 (m, 2 H), 1.73-1.84 (m, 3 H), 2.40 (td, *J* = 2.8, 16.4 Hz, 1 H), 2.70-2.81 (m, 2 H), 2.99 (ddd, *J* = 1.0, 4.1, 21.2 Hz, 1 H), 3.26-3.32 (m, 1 H), 3.72-3.80 (m, 2 H), 4.24-4.29 (m, 1 H), 5.62-5.66 (m, 1 H), 5.80-5.84 (m, 1 H), 9.80 (t, *J* = 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.0 (t), 27.3 (t), 34.0 (t), 40.7 (t), 44.5 (t), 48.0 (d), 55.0 (d), 65.4 (s), 67.7 (t), 126.6 (d), 134.3 (d), 157.1 (s), 202.0 (d); exact mass *m/z* calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1208.

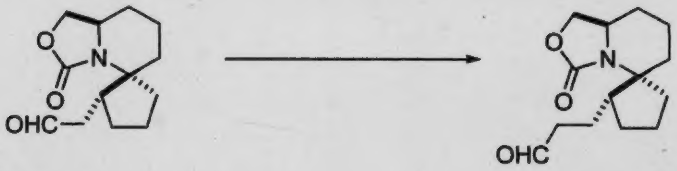
(5'*R*,8'a*R*)-Tetrahydrospiro[(*S*)-2-(2-oxoethyl)cyclopentane-1,5'(1'*H*)oxazolo[3,4-*a*]pyridine]-3'-one (29.3).



29.2 **29.3**

Pd-C (10%, 10 mg) was added to a solution of **29.2** (95.0 mg, 0.40 mmol) in 1:2 EtOH-hexane (5 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (30 psi) for 3.5 h. The mixture was then filtered through a Celite pad (1 x 1.5 cm), using CH_2Cl_2 (20 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 2:3 EtOAc-hexane, gave **29.3** (61.5 mg, 65%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2941, 2719, 1745, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23-1.38 (m, 1 H), 1.46-1.62 (m, 4 H), 1.72-1.96 (m, 7 H), 2.43-2.51 (m, 1 H), 2.69-2.87 (m, 2 H), 3.58-3.64 (m, 1 H), 3.77 (t, *J* = 8.3 Hz, 1 H), 4.26 (dd, *J* = 6.8, 8.0 Hz, 1 H), 9.79 (t, *J* = 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7 (t), 22.6 (t), 28.5 (t), 30.7 (t), 34.7 (t), 36.0 (t), 44.0 (d), 44.5 (t), 55.9 (d), 65.7 (s), 67.9 (t), 157.1 (s), 202.6 (d); exact mass *m/z* calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1361.

(5'*R*,8'a*R*)-Tetrahydrospiro[(*S*)-2-(3-oxopropyl)cyclopentane-1,5'(1'*H*)oxazolo[3,4-*a*]pyridine]-3'-one (29.4).

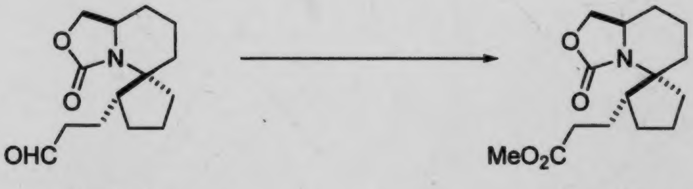


29.3 **29.4**

KHMDS (0.5 M in PhMe, 0.4 mL, 0.2 mmol) was added dropwise to a stirred and cooled (0 °C) solution of $Ph_3PCH_2(OCH_3)Cl$ (85 mg, 0.22 mmol) in PhMe (2 mL). The ice bath was removed and stirring was continued for 30 min. The mixture was cooled to 0 °C and aldehyde **29.3** (16 mg, 0.067 mmol) in PhMe (1 mL) was added dropwise over ca. 2 min. The mixture was stirred at room temperature for 10 h. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Dilute hydrochloric acid (3 N, 3 mL) and acetone (3 mL) were added to the residue, and the mixture was heated at reflux for 3.5 h, cooled, and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 EtOAc-hexane, gave aldehyde **29.4** (13 mg, 78%) as a colorless oil: FTIR ($CDCl_3$ cast) 2942, 2868, 1747, 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23-1.64 (m, 5 H), 1.70-1.99 (m, 10 H), 2.36-2.56 (m, 2 H), 3.58-3.66 (m, 1 H), 3.77 (t, *J* = 8.0 Hz, 1 H), 4.24 (dd, *J* = 6.7, 7.9 Hz, 1 H), 9.77 (t, *J* = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.5 (t), 21.3 (t), 28.4 (t), 29.4 (t), 43.6 (t), 55.9 (d), 65.7

(s), 67.7 (t), 157.0 (s), 203.1 (d); exact mass *m/z* calcd for $C_{14}H_{21}NO_3$ 251.1522, found 251.1525.

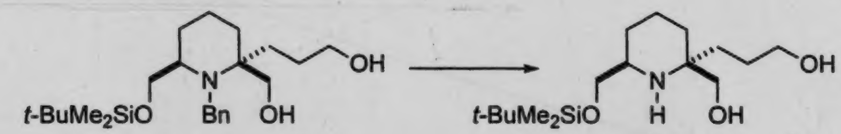
(5'*R*,8'a*R*)-Tetrahydrospiro[(*S*)-2-[(2-methoxycarbonyl)-ethyl)]cyclopentane-1,5'(1'*H*)oxazolo[3,4-*a*]pyridine]-3'-one (29.5).



29.4 **29.5**

NIS (150 mg, 0.63 mmol) and K_2CO_3 (88 mg, 0.63 mmol) were added, each in one portion, to a stirred solution of aldehyde **29.4** (40 mg, 0.16 mmol) in MeOH (5 mL). The mixture was stirred for 10 h with protection from light and then the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:4 EtOAc-hexane, gave ester **29.5** (31 mg, 68%) as a colorless oil: FTIR ($CDCl_3$ cast) 2947, 1746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23-1.66 (m, 6 H), 1.71-1.87 (m, 7 H), 1.88-2.00 (m, 2 H), 2.26-2.35 (m, 2 H), 2.37-2.46 (m, 1 H), 3.57-3.64 (m, 1 H), 3.64 (s, 3 H), 3.75 (t, *J* = 8.2 Hz, 1 H), 4.24 (dd, *J* = 6.8, 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.6 (t), 24.1 (t), 28.4 (t), 29.6 (t), 51.4 (q), 56.0 (d), 65.7 (s), 67.7 (t), 157.1 (s), 174.3 (s); exact mass *m/z* calcd for $C_{15}H_{23}NO_4$ 281.1627, found 281.1629.

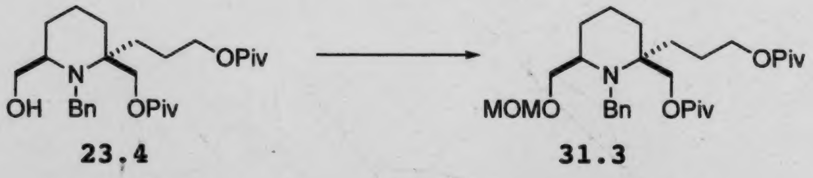
3-[(2*R*,6*R*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-2-(hydroxymethyl)piperidin-2-yl]propan-1-ol (31.2).



42.1 **31.2**

Pd-C (10%, 20 mg) was added to a solution of diol **42.1** (0.600 g, 1.47 mmol) in 2:1 EtOAc-MeOH (15 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (30 psi) for 2 h. The mixture was filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (100 mL) as a rinse, and the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave amine **31.2** (0.465 g, 100%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3316, 2929, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 0.98-1.09 (m, 1 H), 1.35-1.42 (m, 1 H), 1.46-1.81 (m, 8 H), 2.84-2.94 (m, 4 H), 3.38 (AB q, J = 10.4 Hz, $\Delta\nu_{AB}$ = 58.2 Hz, 2 H), 3.43 (dd, J = 6.8, 9.6 Hz, 1 H), 3.59 (dd, J = 4.0, 9.8 Hz, 1 H), 3.59-3.68 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.41 (q), -5.36 (q), 18.2 (s), 19.6 (t), 25.9 (q), 26.8 (t), 27.7 (t), 29.5 (t), 30.5 (t), 51.6 (d), 54.8 (t), 63.1 (s), 67.5 (t), 68.3 (t); exact mass *m/z* calcd for $C_{16}H_{35}NO_3Si$ 317.2386, found 317.2377.

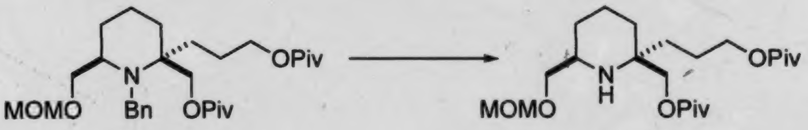
3-[(2*R*,6*R*)-1-Benzyl-6-[(methoxymethoxy)methyl]-2-[(pivaloyloxy)methyl]piperidin-2-yl]propyl Pivaloate (31.3).



23.4 **31.3**

MOMCl (0.14 mL, 1.65 mmol) was added dropwise over ca. 2 min to a stirred and cooled (0 °C) solution of **23.4** (0.320 g, 0.69 mmol) and *i*-Pr_2NEt (0.36 mL, 2.06 mmol) in CH_2Cl_2 (10 mL). The ice bath was left in place but not recharged and stirring was continued for 10 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:9 EtOAc-hexane, gave **31.3** (0.303 g, 87%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2957, 1728, 1493 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (s, 18 H), 1.52-1.85 (m, 10 H), 2.97 (s, 1 H), 3.21 (s, 3 H), 3.33 (t, J = 8.1 Hz, 1 H), 3.56 (dd, J = 3.3, 9.6 Hz, 1 H), 3.88-4.08 (m, 6 H), 4.37 (s, 2 H), 7.17 (t, J = 7.1 Hz, 1 H), 7.23-7.30 (m, 2 H), 7.35 (d, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.7 (t), 22.9 (t), 27.1 (q), 27.2 (q), 28.1 (t), 28.3 (t), 30.4 (t), 38.7 (s), 38.8 (s), 50.6 (t), 55.1 (d), 55.4 (q), 58.2 (s), 64.7 (t), 68.2 (t), 69.5 (t), 96.4 (t), 126.3 (d), 126.9 (d), 128.1 (d), 141.9 (s), 178.5 (s), 178.8 (s); exact mass *m/z* calcd for $C_{29}H_{47}NO_6$ (M - CH_3O) 474.3220, found 474.3208.

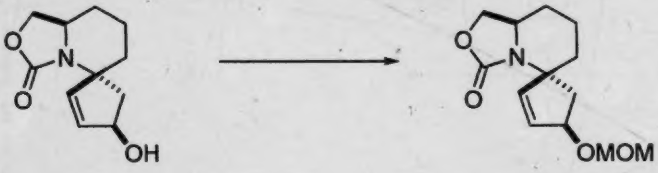
3-[(2*R*,6*R*)-6-[(Methoxymethoxy)methyl]-2-[(pivaloyloxy)methyl]piperidin-2-yl]propyl Pivaloate (31.4).



31.3 **31.4**

Pd-C (10%, 10 mg) was added to a solution of **31.3** (0.296 g, 0.59 mmol) in EtOAc (10 mL) in a Parr bottle. The resulting mixture was hydrogenated (30 psi) for 2 h and then filtered through a Celite pad (1 x 2.5 cm), using CH_2Cl_2 (10 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 2:3 EtOAc-hexane, gave **31.4** (0.230 g, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2935, 2872, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.02-1.08 (m, 1 H), 1.18 (s, 9 H), 1.20 (s, 9 H), 1.26-1.35 (m, 1 H), 1.48-1.58 (m, 5 H), 1.62-1.69 (m, 3 H), 1.86 (s, 1 H), 2.90-2.98 (m, 1 H), 3.29 (t, J = 8.3 Hz, 1 H), 3.33 (s, 3 H), 3.47 (dd, J = 3.5, 9.2 Hz, 1 H), 3.85 (AB q, J = 10.8 Hz, $\Delta\nu_{AB}$ = 80.6 Hz, 2 H), 4.04 (t, J = 6.4 Hz, 2 H), 4.60 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.5 (t), 23.1 (t), 27.2 (q), 28.4 (t), 31.2 (t), 38.7 (s), 38.9 (s), 49.3 (d), 53.6 (t), 55.2 (q), 64.6 (t), 71.1 (t), 72.7 (t), 96.6 (t), 178.0 (s), 178.4 (s); exact mass *m/z* calcd for $C_{21}H_{38}NO_6$ 400.2699, found 400.2690.

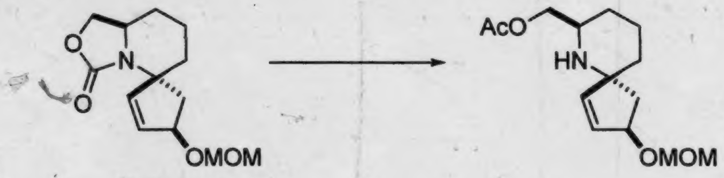
(5'*R*,8'a*R*)-Tetrahydrospiro[(*R*)-4-methoxymethoxy]cyclopent-2-ene-1,5'(1'*H*)oxazolo[3,4-*a*]pyridine]-3'-one (32.1).



26.2 **32.1**

i-Pr_2NEt (0.05 mL, 0.277 mmol), followed by MOMCl (0.011 mL, 0.135 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **26.2** (9.4 mg, 0.045 mmol) in CH_2Cl_2 (2 mL). The ice bath was removed and stirring was continued for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave **32.1** (8.4 mg, 74%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28-1.37 (m, 1 H), 1.58-1.68 (m, 3 H), 1.85-1.92 (m, 2 H), 2.08-2.17 (m, 2 H), 3.38 (s, 3 H), 3.63-3.70 (m, 1 H), 3.79 (t, *J* = 8.8 Hz, 1 H), 4.35 (t, *J* = 8.1 Hz, 1 H), 4.67 (s, 2 H), 4.78 (td, *J* = 2.3, 6.7 Hz, 1 H), 5.95 (dd, *J* = 2.4, 5.7 Hz, 1 H), 6.28 (dd, *J* = 0.4, 5.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.7 (t), 29.5 (t), 37.2 (t), 40.4 (t), 54.6 (q), 55.3 (d), 67.5 (s), 67.9 (t), 81.5 (d), 96.1 (t), 129.9 (d), 140.5 (d), 156.0 (s).

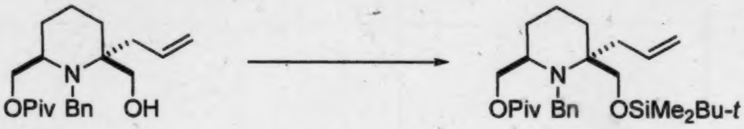
(3*R*,5*R*,7*R*)-[6-Aza-3-(methoxymethoxy)spiro[4,5]dec-1-en-7-yl]methyl Acetate (32.2).



32.1 **32.2**

Me_3SiOK (20 mg, 0.156 mmol) was added to a stirred solution of **32.1** (8.4 mg, 0.033 mmol) in THF (3 mL). The resulting mixture was heated at reflux (65 °C) for 10 h (TLC showed complete consumption of starting material) and cooled. EtOAc (5 mL), followed by water (5 mL) was added and the mixture was extracted with EtOAc (4 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using MeOH, gave **32.2** (8.2 mg, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2930, 1743, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03-1.18 (m, 1 H), 1.46-1.65 (m, 5 H), 1.74-1.82 (m, 1 H), 1.92-1.99 (m, 1 H), 2.06 (s, 3 H), 2.11-2.19 (m, 1 H), 2.90-2.99 (m, 1 H), 3.40 (s, 3 H), 3.75-3.84 (m, 1 H), 4.03-4.12 (m, 1 H), 4.68 (s, 2 H), 4.75-4.83 (m, 1 H), 5.80-5.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.9 (q), 21.3 (t), 27.9 (t), 36.5 (t), 41.4 (t), 51.4 (q), 55.2 (d), 66.9 (s), 69.0 (t), 81.9 (d), 95.9 (t), 131.5 (d), 143.6 (d), 170.8 (s); exact mass *m/z* calcd for $C_{14}H_{23}NO_4$ 269.1627, found 269.1624.

[(2*R*,6*R*)-6-Allyl-1-benzyl-6-[(*tert*-butyldimethylsilyloxy)methyl]piperidin-2-yl]methyl Pivaloate (34.1).

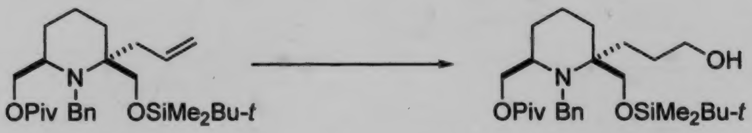


22.2 **34.1**

t-$BuMe_2SiCl$ (0.43 g, 2.77 mmol) was added in one portion to a stirred and cooled (0 °C) solution of alcohol **22.2** (0.76 g, 2.12 mmol), imidazole (0.26 g, 3.82 mmol) and DMAP (10 mg) in CH_2Cl_2 (20 mL). Stirring was continued at 0 °C for 30 min, and at room temperature for 48 h. The reaction mixture was then quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:19 EtOAc-hexane, gave **34.1** (0.82 g, 82%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3063, 2955, 1732, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.14 (s, 3 H), -0.04 (s, 3 H), 0.83 (s, 9 H), 1.12 (s, 9 H), 1.25-1.44 (m, 3 H), 1.53-1.72 (m, 3 H), 2.43-2.56 (m, 2 H), 2.92 (septet, *J* = 4.1 Hz, 1 H), 3.50 (AB q, *J* = 10.3 Hz, $\Delta\nu_{AB}$ = 47.9 Hz, 2 H), 3.70 (dd, *J* = 7.7, 11.0 Hz, 1 H), 4.10 (AB q, *J* = 16.9 Hz, $\Delta\nu_{AB}$ = 299.5 Hz, 2 H), 4.14 (dd, *J* = 3.6, 11.0 Hz, 1 H), 5.02-5.11 (m, 2 H), 5.80-5.90 (m, 1 H), 7.14 (t, *J* = 7.3 Hz, 1 H), 7.25 (t, *J* = 7.8 Hz, 2 H), 7.37 (d, *J* = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.92 (q), -5.90 (q), 18.06 (s), 18.12 (t), 25.8 (q), 27.1 (q), 29.0 (t), 31.3 (t), 34.2 (s), 51.7 (t), 56.3 (d), 59.8 (s), 65.7 (t), 69.6 (t), 116.9 (t), 125.89 (d), 126.9 (d), 128.0 (d), 135.5 (d), 143.2 (s), 178.2 (s);

exact mass (electrospray) *m/z* calcd for $C_{28}H_{48}NO_3Si$ (M + H) 474.3398, found 474.3395.

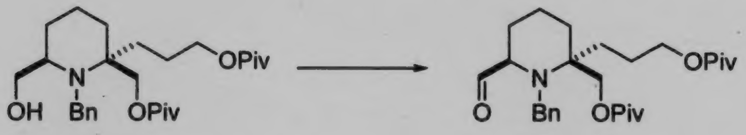
[(2*R*,6*R*)-1-Benzyl-6-[(*tert*-butyldimethylsilyloxy)-methyl]-6-(3-hydroxypropyl)piperidin-2-yl]methyl Pivaloate (34.2).



34.1 **34.2**

9-BBN (0.5 M in THF, 5.0 mL, 2.5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **34.1** (0.798 g, 1.68 mmol) in THF (20 mL). After addition, the ice-bath was removed and stirring was continued for 10 h. The mixture was cooled to 0 °C, slowly quenched by addition of MeOH (2 mL), and then aqueous NaOH (2N, 10 mL) and H_2O_2 (30%, 3 mL) were added. The ice-bath was left in place but not recharged and stirring was continued for 2 h. The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:19 to 1:4 EtOAc-hexane, gave alcohol **34.2** (0.684 g, 83%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3382, 2954, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.16 (s, 3 H), -0.05 (s, 3 H), 0.82 (s, 9 H), 1.12 (s, 9 H), 1.37-1.45 (m, 3 H), 1.52-1.68 (m, 6 H), 1.72-1.78 (m, 2 H), 2.98 (septet, *J* = 4.1 Hz, 1 H), 3.50 (AB q, *J* = 10.3 Hz, $\Delta\nu_{AB}$ = 27.0 Hz, 2 H), 3.64 (s, 2 H), 3.72 (dd, *J* = 7.7, 11.0 Hz, 1 H), 4.05 (AB q, *J* = 17.1 Hz, $\Delta\nu_{AB}$ = 215.3 Hz, 2 H), 4.13 (dd, *J* = 3.9, 11.0 Hz, 1 H), 7.14 (t, *J* = 7.3 Hz, 1 H), 7.25 (t, *J* = 7.7 Hz, 2 H), 7.37 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.9 (q), 18.1 (s), 18.4 (t), 25.3 (t), 25.8 (q), 27.1 (q), 27.3 (t), 28.4 (t), 30.5 (t), 38.6 (s), 51.1 (t), 55.9 (d), 59.7 (s), 63.8 (t), 65.8 (t), 69.8 (t), 125.9 (d), 126.8 (d), 128.0 (d), 143.2 (s), 178.3 (s); exact mass *m/z* calcd for $C_{27}H_{46}NO_4Si$ (M - CH_3) 476.3196, found 476.3197.

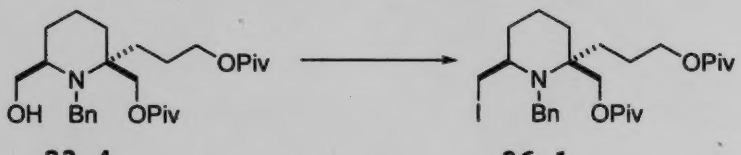
3-[(2*R*,6*R*)-1-Benzyl-2-[(pivaloyloxy)methyl]-6-formylpiperidin-2-yl]propyl Pivaloate (35.1).



23.4 **35.1**

TPAP (14.0 mg, 0.039 mmol) was added to a stirred solution of alcohol **23.4** (37.6 mg, 0.081 mmol) and NMO (19.7 mg, 0.163 mmol) in CH_2Cl_2 (4 mL). Stirring was continued for 5 min and TLC analysis showed that the reaction was completed at this stage. Aldehyde **35.1** was found to epimerize on silica gel and on grade III Al_2O_3, and so it was used crude. A small sample was obtained for characterization by rapid flash chromatography over silica gel, using 1:4 EtOAc-hexane as eluent. Pure aldehyde **35.1** (yellow oil) had: ^{1}H NMR (C_6D_6, 500 MHz) δ 1.07-1.28 (m, 5 H), 1.15 (s, 9 H), 1.17 (s, 9 H), 1.36-1.49 (m, 4 H), 1.58-1.64 (m, 1 H), 3.04-3.08 (m, 1 H), 3.86 (AB q, *J* = 15.6 Hz, $\Delta\nu_{AB}$ = 233.3 Hz, 2 H), 3.95 (dt, *J* = 1.6, 6.2 Hz, 2 H), 4.11 (d, *J* = 1.9 Hz, 2 H), 7.07 (t, *J* = 7.3 Hz, 1 H), 7.17 (t, *J* = 7.4 Hz, 2 H), 7.26 (d, *J* = 7.7 Hz, 2 H), 9.18 (d, *J* = 1.9 Hz, 1 H); ^{13}C NMR (C_6D_6, 125.7 MHz) δ 17.8 (t), 23.3 (t), 24.7 (t), 27.36 (q), 27.39 (q), 28.3 (t), 30.4 (t), 38.8 (s), 38.9 (s), 52.5 (t), 58.1 (s), 64.7 (t), 66.3 (d), 69.0 (t), 127.3 (d), 128.4 (d), 128.7 (d), 140.4 (s), 177.3 (s), 177.7 (s), 202.4 (d); exact mass *m/z* calcd for $C_{27}H_{41}NO_5$ 459.2984, found 459.2978.

3-[(2*R*,6*R*)-1-Benzyl-6-(iodomethyl)-2-[(pivaloyloxy)-methyl]piperidin-2-yl]propyl Pivaloate (36.1).

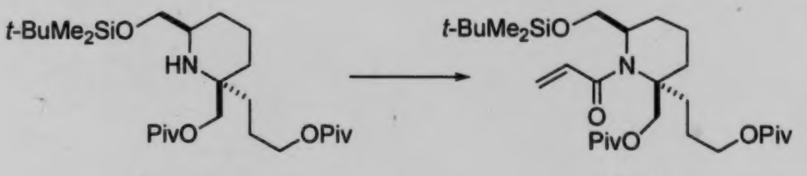


23.4 **36.1**

I_2 (0.40 g, 1.57 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **23.4** (0.59 g, 1.27 mmol), Ph_3P (0.43 g, 1.66 mmol) and imidazole (0.13 g, 1.89 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 3 h, and the mixture was then diluted with Et_2O (50 mL) and washed with aqueous $Na_2S_2O_3$ (10%), water and brine. The organic extract was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:19 EtOAc-hexane, gave **36.1** (0.59 g, 81%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3025, 2968, 1727 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.13 (s, 9 H), 1.14 (s, 9 H), 1.18-1.28 (m, 3 H), 1.38-1.62 (m, 7 H), 2.78 (t, *J* = 9.8 Hz, 1 H), 3.05-3.12 (m, 1 H), 3.23-3.28 (m, 1 H), 3.63 (AB q, *J* = 15.8 Hz, $\Delta\nu_{AB}$ = 30.4 Hz, 2 H), 3.88-3.96 (m, 4 H), 7.07 (t, *J* = 7.2 Hz, 1 H), 7.16-7.25 (m, 4 H); ^{13}C NMR (C_6D_6, 125.7 MHz) δ 8.2 (t), 16.8 (t), 23.0 (t), 27.3 (q), 27.4 (q), 28.2 (t), 30.5 (t), 30.6 (t), 38.9 (s), 50.5 (t), 58.1 (d), 58.5

(t), 64.7 (t), 69.0 (t), 127.2 (d), 127.8 (d), 128.7 (d), 140.7 (s), 177.4 (s), 177.6 (s); exact mass *m/z* calcd for $C_{26}H_{39}INO_4$ (M - CH_3) 556.1924, found 556.1953.

3-[(2*R*,6*R*)-1-Acryloyl-6-[(*tert*-butyldimethylsilyloxy)-methyl]-2-[(pivaloyloxy)methyl]piperidin-2-yl]propyl Pivaloate (38.1).

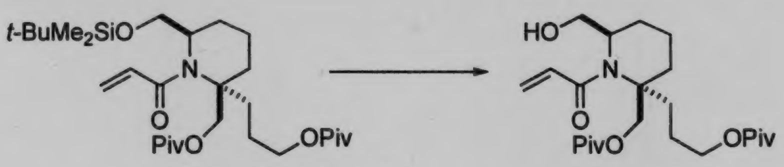


31.1 **38.1**

Acryloyl chloride (0.06 mL, 0.74 mmol) was added dropwise over ca. 2 min to a stirred and cooled (0 °C) solution of amine **31.1** (115 mg, 0.24 mmol), Et_3N (0.17 mL, 1.22 mmol) and DMAP (5 mg) in CH_2Cl_2 (15 mL). Stirring was continued for 10 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL) and then extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:9 EtOAc-hexane, gave amide **38.1** (38 mg, 29%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 6 H), 0.88 (s, 9 H), 1.18 (s, 18 H), 1.41-1.70 (m, 7 H), 1.71-1.79 (m, 1 H), 1.90 (dt, *J* = 4.0, 13.0 Hz, 1 H), 1.99-2.07 (m, 1 H), 2.37 (dt, *J* = 5.0, 13.0 Hz, 1 H), 3.55 (dd, *J* = 5.4, 9.8 Hz, 1 H), 3.65 (t, *J* = 9.5 Hz, 1 H), 3.95-4.08 (m, 3 H), 4.39 (AB q, *J* = 10.5 Hz, $\Delta\nu_{AB}$ = 179.1 Hz, 2 H), 5.61 (dd, *J* = 1.9, 10.5 Hz, 1 H), 6.18 (dd, *J* = 1.9, 6.7 Hz, 1 H), 6.61 (dd, *J* = 10.4, 16.7 Hz, 1 H); ^{13}C

NMR ($CDCl_3$, 125.7 MHz) δ -5.5 (q), -5.4 (q), 13.8 (t), 18.2 (s), 22.4 (t), 23.4 (t), 25.8 (q), 27.2 (q), 29.1 (t), 31.9 (t), 38.7 (s), 38.8 (s), 55.0 (d), 59.4 (s), 64.5 (t), 65.4 (t), 65.8 (t), 126.8 (t), 130.7 (d), 168.8 (s), 178.0 (s), 178.4 (s).

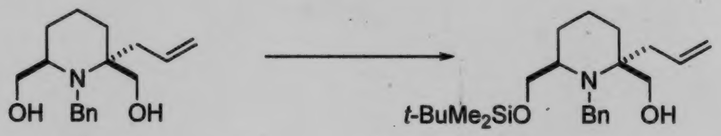
3-[(2*R*,6*R*)-1-Acryloyl-6-(hydroxymethyl)-2-[(pivaloyloxy)methyl]piperidin-2-yl]propyl Pivaloate (38.2).



38.1 **38.2**

TBAF (1.0 M in THF, 0.3 mL, 0.30 mmol) was added to a stirred solution of amide **38.1** (37 mg, 0.07 mmol) in THF (5 mL). Stirring was continued for 10 h and the solvent was concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:3 EtOAc-hexane, gave alcohol **38.2** (12 mg, 41%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.187 (s, 9 H), 1.189 (s, 9 H), 1.46-1.85 (m, 7 H), 1.92-1.99 (m, 2 H), 2.03 (dd, *J* = 4.0, 12.8 Hz, 1 H), 2.30 (dt, *J* = 4.9, 13.0 Hz, 1 H), 3.66-3.76 (m, 2 H), 4.04 (t, *J* = 6.4 Hz, 2 H), 4.07-4.12 (m, 1 H), 4.43 (AB q, *J* = 10.8 Hz, Δv_{AB} = 252.3 Hz, 2 H), 5.61 (dd, *J* = 1.9, 10.5 Hz, 1 H), 6.18 (dd, *J* = 1.9, 6.8 Hz, 1 H), 6.69 (dd, *J* = 10.6, 16.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.7 (t), 22.6 (t), 23.6 (t), 27.2 (q), 28.5 (t), 31.8 (t), 38.8 (s), 54.7 (d), 59.6 (s), 64.4 (t), 65.5 (t), 66.3 (t), 126.9 (t), 131.1 (d), 169.2 (s), 178.2 (s), 178.5 (s).

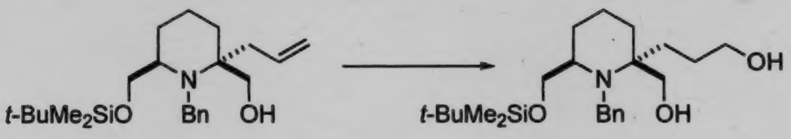
[(2*R*,6*R*)-2-Allyl-1-benzyl-6-[(*tert*-butyldimethylsilyloxy)methyl]piperidin-2-yl]methanol (41.1).



22.1 **41.1**

t-BuMe$_2$SiCl (0.221 g, 1.42 mmol) was added in one portion to a stirred solution of diol **22.1** (0.489 g, 1.78 mmol), imidazole (0.200 g, 2.94 mmol) and DMAP (10 mg) in CH$_2$Cl$_2$ (20 mL). Stirring was continued at room temperature for 10 min and the solution became cloudy. Another portion of *t*-BuMe$_2$SiCl (0.097 g, 0.62 mmol) was added and stirring was continued for 30 min. The reaction mixture was quenched by addition of saturated aqueous NH$_4$Cl (20 mL), washed with brine, dried (MgSO$_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:9 EtOAc-hexane, gave **41.1** (0.602 g, 87%) as a colorless oil: FTIR (CH$_2$Cl$_2$ cast) 3458, 3063, 3024, 2928, 1637 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ -0.12 (s, 3 H), -0.10 (s, 3 H), 0.80 (s, 9 H), 1.30-1.40 (m, 1 H), 1.54-1.70 (m, 3 H), 1.73-1.82 (m, 1 H), 1.91-1.98 (m, 1 H), 2.27 (dd, *J* = 7.4, 13.6 Hz, 1 H), 2.46 (d, *J* = 5.0 Hz, 1 H), 2.61 (dd, *J* = 7.6, 13.7 Hz, 1 H), 2.79-2.87 (m, 1 H), 3.22 (dd, *J* = 7.2, 10.1 Hz, 1 H), 3.49-3.58 (m, 2 H), 3.90 (AB q, *J* = 16.9 Hz, $\Delta\nu_{AB}$ = 252.3 Hz, 2 H), 5.04-5.13 (m, 2 H), 5.71-5.81 (m, 1 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.36 (d, *J* = 7.3 Hz, 2 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ -5.6 (q). -5.5 (q), 18.2 (s), 18.5 (t), 25.9 (q), 29.1 (t), 30.0 (t), 33.3 (t), 51.6 (t), 60.1 (d), 61.2 (s), 66.9 (t), 67.4 (t), 117.7 (s), 126.4 (d), 126.6 (d), 128.4 (d), 134.4 (d), 142.7 (s); exact mass *m/z* calcd for $C_{22}H_{36}NOSi$ (M - OCH_3) 358.2566, found 358.2566.

3-[(2*R*,6*R*)-1-Benzyl-6-[(*tert*-butyldimethylsilyloxy)-methyl]-2-(hydroxymethyl)piperidin-2-yl]propan-1-ol (42.1).

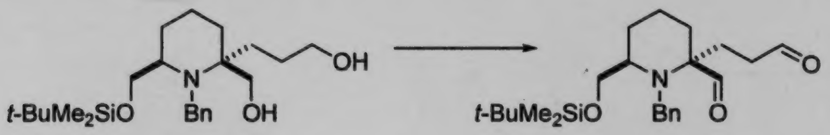


41.1 **42.1**

9-BBN (0.5 M in THF, 8.0 mL, 4.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **41.1** (0.600 g, 1.54 mmol) in THF (20 mL). After addition, the ice-bath was removed and stirring was continued for 10 h. The mixture was cooled to 0 °C, slowly quenched by addition of MeOH (2 mL), and then aqueous NaOH (2N, 5 mL) and H_2O_2 (30%, 2 mL) were added. The ice-bath was left in place but not recharged and stirring was continued for 2 h. The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:4 EtOAc-hexane to EtOAc, gave diol **42.1** (0.601 g, 96%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3355, 3083, 2951, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.13 (s, 3 H), -0.12 (s, 3 H), 0.80 (s, 9 H), 1.27-1.93 (m, 11 H), 2.66 (s, 1 H), 2.86 (s, 1 H), 3.22 (dd, *J* = 7.4, 9.6 Hz, 1 H), 3.39 (AB q, *J* = 11.2 Hz, $\Delta\nu_{AB}$ = 64.0 Hz, 2 H), 3.52 (dd, *J* = 4.4, 10.1 Hz, 1 H), 3.59-3,69 (m, 3 H), 4.14 (d, *J* = 16.9 Hz, 1 H), 7.18 (t, *J*

= 7.3 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 2 H), 7.36 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.60 (q). -5.56 (q), 18.2 (s), 18.6 (t), 24.7 (t), 25.9 (q), 27.3 (t), 28.5 (t), 29.6 (t), 33.3 (t), 51.3 (t), 59.7 (d), 60.8 (s), 63.3 (t), 67.0 (t), 67.2 (t), 126.4 (d), 126.6 (d), 128.4 (d), 142.7 (s); exact mass *m/z* calcd for $C_{23}H_{40}NO_3Si$ (M - H) 406.2777, found 406.2785.

(2*R*,6*R*)-1-Benzyl-6-[(*tert*-butyldimethylsilyloxy)-methyl]-2-(2-formylethyl)piperidine-2-carbaldehyde (42.2).

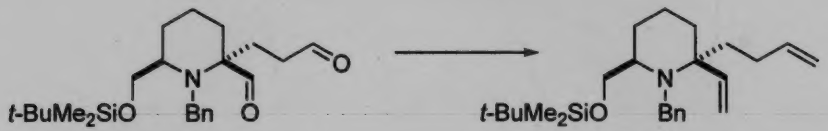


42.1 **42.2**

DMSO (3.0 mL, 42.27 mmol) in CH_2Cl_2 (7.0 mL) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (3.5 mL, 39.32 mmol) in CH_2Cl_2 (60 mL). Stirring was continued for 30 min, and diol **42.1** (4.81 g, 11.83 mmol) in CH_2Cl_2 (10 mL) was added dropwise over ca. 10 min, a further portion of CH_2Cl_2 (5 mL) being used as a rinse. Stirring at -78 °C was continued for 1 h, and Et_3N (10.0 mL, 71.75 mmol) was added dropwise over ca. 5 min. Stirring was continued for 1 h, the dry-ice bath was removed, and stirring was continued for 10 h. Saturated aqueous NH_4Cl (80 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 1:9 EtOAc-hexane, gave aldehyde **42.2** (3.98 g, 84%) as a yellow oil: FTIR (CH_2Cl_2

cast) 3062, 2951, 2856, 2714, 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ -0.13 (s, 3 H), -0.12 (s, 3 H), 0.79 (s, 9 H), 1.38-1.54 (m, 3 H), 1.67-1.86 (m, 3 H), 1.98-2.13 (m, 2 H), 2.38-2.47 (m, 1 H), 2.67-2.76 (m, 1 H), 2.87 (septet, *J* = 4.0 Hz, 1 H), 3.10 (dd, *J* = 7.8, 10.1 Hz, 1 H), 3.54 (dd, *J* = 4.5, 10.1 Hz, 1 H), 3.85 (s, s, 2 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 2 H), 7.36 (d, *J* = 7.2 Hz, 2 H), 9.49 (d, *J* = 0.7 Hz, 1 H), 9.76 (t, *J* = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.61 (q), -5.60 (q), 17.9 (t), 18.2 (s), 20.2 (t), 25.9 (q), 27.6 (t), 27.9 (t), 38.9 (t), 53.5 (s), 58.1 (d), 65.2 (t), 67.8 (t), 126.7 (d), 126.8 (d), 128.2 (d), 141.6 (s), 201.3 (d), 204.5 (d); exact mass *m/z* calcd for $C_{23}H_{37}NO_3Si$ 403.2543, found 403.2541.

(2*R*,6*R*)-1-Benzyl-6-[(*tert*-butyldimethylsilyloxy)-methyl]-2-(but-3-enyl)-2-vinylpiperidine (42.3).

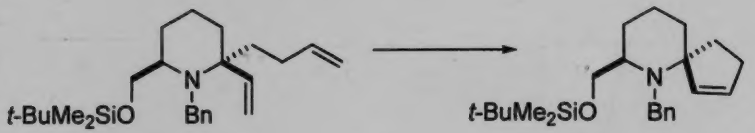


42.2 **42.3**

KHMDS (0.5 M in PhMe, 47.0 mL, 23.50 mmol) was added dropwise to a cooled (0 °C) and stirred solution of Ph_3PCH_3Br (9.36 g, 25.69 mmol) in PhMe (70 mL). The ice bath was removed and stirring was continued for 1 h. The reddish mixture was cooled to 0 °C and aldehyde **42.2** (3.98 g, 9.88 mmol) in PhMe (20 mL) was added dropwise over ca. 10 min. The cold bath was removed and stirring was continued for 10 h. Saturated aqueous NH_4Cl (100 mL) was added, and the mixture was extracted with Et_2O (3 x 150 mL). The combined organic extracts were washed with brine, dried

($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 1:19 EtOAc-hexane, gave diene **42.3** (3.44 g, 87%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3080, 2950, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.11 (s, 3 H), -0.10 (s, 3 H), 0.80 (s, 9 H), 1.38-1.48 (m, 1 H), 1.55-1.87 (m, 7 H), 2.02-2.22 (m, 2 H), 2.96 (septet, *J* = 4.0 Hz, 1 H), 3.15 (dd, *J* = 8.4, 9.7 Hz, 1 H), 3.60 (dd, *J* = 4.3, 9.9 Hz, 1 H), 3.79 (AB q, *J* = 16.5 Hz, $\Delta\nu_{AB}$ = 97.6 Hz, 2 H), 4.93-5.08 (m, 4 H), 5.80-5.93 (m, 2 H), 7.17 (t, *J* = 7.3 Hz, 1 H), 7.27 (t, *J* = 7.4 Hz, 2 H), 7.37 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.53 (q), -5.50 (q), 18.2 (s), 19.1 (t), 25.9 (q), 26.1 (t), 28.4 (t), 31.3 (t), 32.5 (t), 50.6 (s), 58.0 (d), 61.4 (t), 65.6 (t), 112.9 (t), 114.0 (t), 125.9 (d), 126.9 (d), 127.9 (d), 139.3 (t), 143.9 (s), 145.3 (d); exact mass *m/z* calcd for $C_{25}H_{41}NOSi$ (M - H) 398.2879, found 398.2876.

tert-Butyldimethyl[[(5*R*,7*R*)-[6-aza-6-benzylspiro[4,5]-dec-1-en-7-yl]methyl]oxy]silane (43.1).

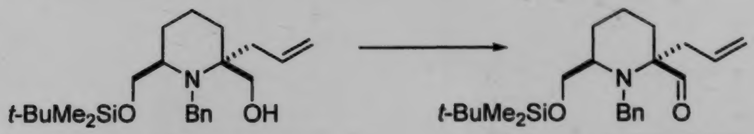


42.3 **43.1**

Grubbs II catalyst (**23.11**) (3 mg, 5 mol%) was added to a solution of diene **42.3** (9.2 mg, 0.023 mmol) in $ClCH_2CH_2Cl$ (1 mL) and the mixture was heated at 70 °C for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:19 EtOAc-hexane, gave **43.1** (8.0 mg, 94%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3083, 2954, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz)

δ -0.14 (s, 6 H), 0.78 (s, 9 H), 1.15-1.26 (m, 1 H), 1.44-1.73 (m, 4 H), 1.84 (t, J = 6.4 Hz, 2 H), 1.90-1.96 (m, 1 H), 2.34-2.42 (m, 2 H), 2.48-2.58 (m, 1 H), 2.86 (dd, J = 8.2, 9.9 Hz, 1 H), 3.52 (dd, J = 4.0, 10.0 Hz, 1 H), 3.65 (AB q, J = 16.4 Hz, $\Delta\nu_{AB}$ = 232.5 Hz, 2 H), 5.50-5.53 (m, 1 H), 5.62-5.66 (m, 1 H), 7.13 (t, J = 7.3 Hz, 1 H), 7.24 (t, J = 7.8 Hz, 2 H), 7.33 (d, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.543 (q), -5.535 (q), 18.2 (s), 20.8 (t), 25.9 (q), 26.2 (t), 30.5 (t), 31.7 (t), 37.3 (t), 53.3 (s), 62.2 (d), 67.3 (t), 74.1 (t), 125.7 (d), 126.8 (d), 127.8 (d), 130.2 (d), 139.9 (d), 144.3 (s); exact mass *m/z* calcd for $C_{23}H_{37}NOSi$ 371.2644, found 371.2638.

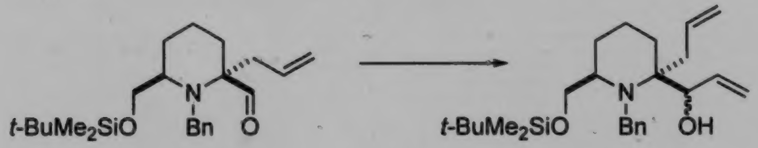
(2*R*,6*R*)-2-Allyl-1-benzyl-6-[(*tert*-butyldimethylsilyloxy)methyl]piperidine-2-carbaldehyde (46.1).



41.1 **46.1**

DMSO (0.30 mL, 4.22 mmol) in CH_2Cl_2 (0.70 mL) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.30 mL, 3.37 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 30 min, and alcohol **41.1** (0.907 g, 2.33 mmol) in CH_2Cl_2 (10 mL) was added dropwise over ca. 10 min, a further portion of CH_2Cl_2 (4 mL) being used as a rinse. Stirring at -78 °C was continued for 1 h, and Et_3N (0.80 mL, 5.74 mmol) was added dropwise over ca. 5 min. Stirring was continued for 1 h, the dry-ice bath was removed, and stirring was continued for 10 h. The mixture was filtered through a short column of silica gel (2.5 x 5 cm), using 1:4 EtOAc-hexane (100 mL) as a rinse. Evaporation of the solvent gave the crude aldehyde **46.1** as a yellow oil. The aldehyde was unstable to flash chromatography, and so it was used in the next step without further purification. However, a small amount of pure **46.1** was obtained by flash chromatography (silica gel, 1:19 EtOAc-hexane) and had: FTIR (CH_2Cl_2 cast) 3063, 2952, 2856, 2804, 2708, 1730, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.12 (s, 3 H), -0.11 (s, 3 H), 0.80 (s, 9 H), 1.35-1.45 (m, 1 H), 1.52-1.60 (m, 2 H), 1.64-1.78 (m, 2 H), 1.83-1.91 (m, 1 H), 2.47 (dd, J = 8.5, 14.1 Hz, 1 H), 2.59 (dd, J = 6.1, 14.1 Hz, 1 H), 2.86 (septet, J = 4.0 Hz, 1 H), 3.09 (dd, J = 8.0, 10.0 Hz, 1 H), 3.56 (dd, J = 4.4, 10.1 Hz, 1 H), 3.87 (s, 2 H), 5.06-5.14 (m, 2 H), 5.84-5.92 (m, 1 H), 7.20 (t, J = 7.3 Hz, 1 H), 7.28 (t, J = 7.4 Hz, 2 H), 7.37 (d, J = 7.7 Hz, 2 H), 9.51 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.6 (q), 17.6 (t), 18.2 (s), 25.9 (q), 27.9 (t), 28.7 (t), 33.4 (t), 53.9 (t), 58.3 (d), 65.5 (t), 68.5 (s), 117.7 (t), 126.6 (d), 126.8 (d), 128.2 (d), 133.9 (d), 141.9 (s), 204.5 (d); exact mass (electrospray) *m/z* calcd for $C_{23}H_{38}NO_2Si$ (M + H) 388.2672, found 388.2673.

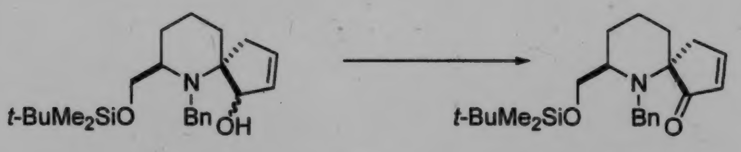
1-[(2*R*,6*R*)-2-Allyl-1-benzyl-6-[(*tert*-butyldimethylsilyloxy)methyl]piperidin-2-yl]prop-2-en-1-ol (46.2).



46.1 **46.2**

Vinylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol) was added dropwise over ca. 5 min to a stirred and cooled (-20 °C) solution of aldehyde **46.1** (crude from previous step, assumed to be 2.33 mmol) in THF (40 mL). Stirring was continued for 30 min and saturated aqueous NH_4Cl (30 mL) was then added. The reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:9 EtOAc-hexane, gave alcohol **46.2** (0.789 g, 81.5% over 2 steps) as a yellow oil: FTIR ($CDCl_3$ cast) 3369, 3072, 2951, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.11 (s, 3 H), -0.09 (s, 3 H), 0.81 (s, 9 H), 1.41-1.84 (m, 6 H), 2.42 (dd, J = 7.1, 14.7 Hz, 1 H), 2.66 (dd, J = 7.4, 14.7 Hz, 1 H), 2.85 (quintet, J = 6.1 Hz, 1 H), 3.36 (dd, J = 7.9, 10.1 Hz, 1 H), 3.49 (s, 1 H), 3.60 (dd, J = 5.7, 10.1 Hz, 1 H), 4.10 (AB q, J = 16.3 Hz, $\Delta\nu_{AB}$ = 207.4 Hz, 2 H), 4.15 (d, J = 5.1 Hz, 1 H), 5.04-5.15 (m, 3 H), 5.28 (td, J = 1.8, 17.1 Hz, 1 H), 5.86-5.98 (m, 1 H), 6.01-6.10 (m, 1 H), 7.16-7.21 (m, 1 H), 7.26-7.36 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.6 (q), -5.5 (q), 17.3 (t), 18.2 (s), 25.6 (t), 25.9 (q), 30.7 (t), 35.4 (t), 53.7 (t), 58.4 (d), 62.9 (s), 66.7 (t), 77.5 (d), 115.2 (t), 117.6 (t), 126.3 (d), 127.2 (d), 128.2 (d), 135.0 (d), 138.2 (d), 142.0 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{42}NO_2Si$ (M + H) 403.2906, found 403.2903.

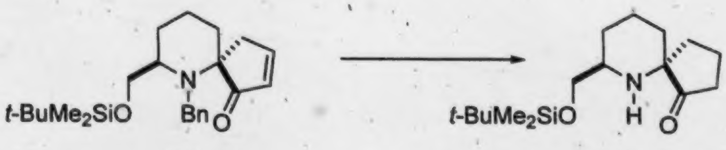
(5*R*,7*R*)-[6-Aza-6-benzyl-7-[(*tert*-butyldimethylsilyloxy)methyl]spiro[4,5]dec-2-en-1-one (46.4).



46.3 **46.4**

DMSO (1.8 mL, 25.50 mmol) in CH_2Cl_2 (3.2 mL) was added dropwise over ca. 10 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (1.9 mL, 21.34 mmol) in CH_2Cl_2 (50 mL). Stirring was continued for 30 min, and alcohol **46.3** (4.20 g, 10.85 mmol) in CH_2Cl_2 (15 mL) was added dropwise over ca. 10 min, a further portion of CH_2Cl_2 (5 mL) being used as a rinse. Stirring at -78 °C was continued for 1 h, and Et_3N (5.0 mL, 35.90 mmol) was added dropwise over ca. 5 min. Stirring was continued for 1 h, the dry-ice bath was removed, and stirring was continued for 10 h. Saturated aqueous NH_4Cl (80 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1:9 EtOAc-hexane, gave aldehyde **46.4** (3.01 g, 72%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3054, 2955, 1699, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.16, (s, 6 H), 0.76 (s, 9 H), 1.23-1.55 (m, 3 H), 1.75-1.85 (m, 2 H), 1.99-2.07 (m, 1 H), 2.49-2.57 (m, 1 H), 2.60-2.67 (m, 1 H), 2.79 (dd, J = 8.7, 9.3 Hz, 1 H), 2.84-2.93 (m, 1 H), 3.37 (AB q, J = 16.0 Hz, $\Delta\nu_{AB}$ = 57.7 Hz, 2 H), 3.52 (dd, J = 4.0, 7.0 Hz, 1 H), 6.19 (td, J = 2.1, 6.0 Hz, 1 H), 7.14 (t, J = 7.6 Hz, 1 H), 7.25 (t, J = 7.8 Hz, 2 H), 7.44 (d, J = 8.0 Hz, 2 H), 7.69-7.74 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.6 (q), 18.2 (s), 20.9 (t), 25.9 (q), 29.9 (t), 34.9 (t), 35.5 (t), 56.2 (t), 63.4 (d), 66.9 (t), 69.3 (s), 126.4 (d), 127.3 (d), 127.9 (d), 133.5 (d), 141.8 (s), 162.5 (d), 210.7 (s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{36}NO_2Si$ (M + H) 386.2510, found 386.2510.

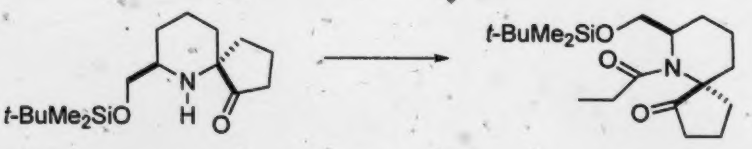
(5*R*,7*R*)-[6-Aza-7-[(*tert*-butyldimethylsilyloxy)methyl]-spiro[4,5]decan-1-one (46.6).



46.4 **46.6**

Pd-C (10%, 0.80 g) was added to a solution of **46.4** (3.00 g, 7.79 mmol) in EtOAc (30 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (46 psi) for 9.5 h. The mixture was then filtered through a Celite pad (1 x 2.5 cm), using EtOAc (150 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 30 cm), using 1:4 to 1:1 EtOAc-hexane, gave amine **46.6** (1.98 g, 86%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3302, 2930, 1743, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.037 (s, 3 H), 0.042 (s, 3 H), 0.89 (s, 9 H), 1.16-1.27 (m, 2 H), 1.45-1.51 (m, 1 H), 1.58-1.88 (m, 6 H), 1.95-2.04 (m, 1 H), 2.23-2.40 (m, 3 H), 2.63-2.70 (m, 1 H), 3.49-3.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.42 (q), -5.38 (q), 18.2 (t), 18.3 (s), 20.6 (t), 25.9 (q), 28.5 (t), 30.2 (t), 33.3 (t), 36.0 (t), 53.3 (d), 64.4 (s), 67.4 (t), 220.0 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{32}NO_2Si$ (M + H) 298.2197, found 298.2199.

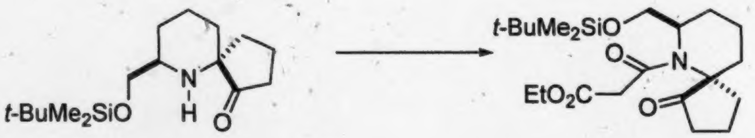
[(5*R*,7*R*)-[6-Aza-7-[(tert-butyldimethylsilyloxymethyl]-1-oxospiro[4,5]decan-6-yl]propan-1-one (48.1).



46.6 **48.1**

Et_3N (0.20 mL, 1.43 mmol), followed by EtCOCl (0.10 mL, 1.15 mmol) was added dropwise over ca. 2 min to a stirred and cooled (0 °C) solution of **46.6** (0.133 g, 0.45 mmol) in CH_2Cl_2 (10 mL). The ice bath was removed and stirring was continued for 10 h. The reaction mixture was diluted with Et_2O (30 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), saturated aqueous NH_4Cl (20 mL), water and brine. The organic extract was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:2 EtOAc-hexane, gave **48.1** (0.140 g, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2954, 1743, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.91 (s, 9 H), 1.10 (t, J = 7.4 Hz, 3 H), 1.45-1.76 (m, 6 H), 1.99-2.25 (m, 5 H), 2.36 (dq, J = 2.2, 7.3 Hz, 2 H), 2.79-2.91 (m, 1 H), 3.66-3.77 (m, 2 H), 3.79-3.85 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.5 (q), -5.4 (q), 9.1 (q), 12.5 (t), 18.1 (s), 18.6 (t), 21.0 (t), 25.7 (t), 25.8 (q), 26.2 (t), 32.5 (t), 34.6 (t), 54.1 (d), 64.0 (s), 65.2 (t), 172.9 (s), 215.3 (s); exact mass m/z calcd for $C_{19}H_{35}NO_3Si$ 353.2386, found 353.2379.

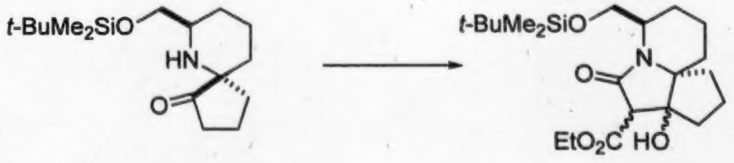
Ethyl [(5*R*,7*R*)-[6-Aza-7-[(*tert*-butyldimethylsilyloxy)-methyl]-1-oxospiro[4,5]decan-6-yl]-3-oxopropanoate (50.2).



46.6 **50.2**

Et_3N (0.10 mL, 0.72 mmol), followed by ethyl 3-chloro-3-oxopropionate (freshly made, 0.05 mL, 0.40 mmol) was added dropwise over ca. 2 min to a stirred and cooled (0 °C) solution of **46.6** (25.0 mg, 0.08 mmol) in CH_2Cl_2 (3 mL). The ice bath was removed and stirring was continued for 3.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 to 1:1 EtOAc-hexane, gave **50.2** (25.0 mg, 72%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2955, 1743, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.10 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.54-1.75 (m, 5 H), 1.79-1.87 (m, 1 H), 1.94-2.01 (m, 1 H), 2.02-2.07 (m, 1 H), 2.08-2.19 (m, 2 H), 2.27-2.35 (m, 1 H), 2.82 (td, J = 10.5, 18.8 Hz, 1 H), 3.29 (d, J = 15.8 Hz, 1 H), 3.69-3.74 (m, 1 H), 3.77-3.87 (m, 3 H), 4.13-4.22 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.6 (q), -5.4 (q), 12.4 (t), 14.1 (q), 18.2 (s), 18.5 (t), 21.5 (t), 25.2 (t), 25.9 (q), 32.0 (t), 34.6 (t), 41.0 (t), 55.0 (d), 61.3 (t), 64.4 (s), 66.3 (t), 165.8 (s), 167.9 (s), 214.7 (s); exact mass m/z calcd for $C_{21}H_{37}NO_5Si$ 411.2441, found 411.2440.

Ethyl (4*R*,10a*R*)-Decahydro-4-[(tert-butyldimethylsilyloxy)methyl]-7a-hydroxy-6-oxocyclopenta[*i*]indolizine-7-carboxylate (50.3).

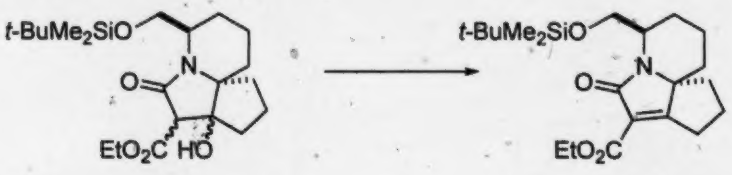


46.6 **50.3**

Et_3N (0.10 mL, 0.72 mmol), followed by ethyl 3-chloro-3-oxo-propionate (freshly made, 0.09 mL, 0.70 mmol) was added dropwise over ca. 2 min to a stirred and cooled (0 °C) solution of **46.6** (84.8 mg, 0.28 mmol) in Acetonitrile (6 mL). The ice bath was removed and stirring was continued for 4 h. Another portion of Et_3N (0.10 mL, 0.72 mmol) was added and the reaction mixture was heated at 45 °C for 10 h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:9 t-BuOMe-CH_2Cl_2, gave two separable alcohols **50.3** (96.0 mg, 71%) as colorless oils. One of the alcohols had: FTIR (CH_2Cl_2 cast) 3424, 2954, 1741, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.33 (t, J = 7.1 Hz, 3 H), 1.25-1.37 (m, 2 H), 1.54-1.84 (m, 5 H), 1.87-2.05 (m, 5 H), 3.14-3.21 (m, 1 H), 3.47 (s, 1 H), 3.60 (s, 1 H), 4.11 (t, J = 9.8 Hz, 1 H), 4.25 (dq, J = 1.9, 7.3 Hz, 2 H), 4.38 (dd, J = 4.0, 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.3 (q), 14.1 (t), 18.3 (s), 21.5 (t), 22.2 (t), 25.9 (q), 28.7 (t), 31.2 (t), 34.3 (t), 41.9 (t), 57.9 (d), 59.0 (d), 62.1 (s), 63.6

(t), 74.1 (t), 81.9 (s), 166.0 (s), 169.8 (s); exact mass (electrospray) *m/z* calcd for $C_{21}H_{37}NNaO_5Si$ (M + Na) 434.2333, found 434.2335.

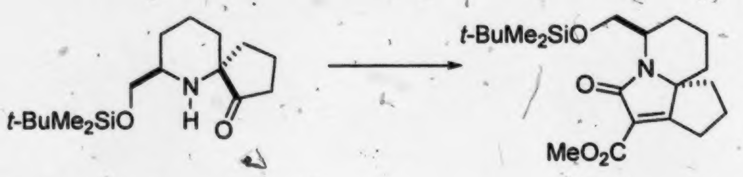
Ethyl (4*R*,10a*S*)-4-[(*tert*-Butyldimethylsilyloxy)-methyl]-1,2,3,4,6,8,9,10-octahydro-6-oxocyclopenta-[*i*]indolizine-7-carboxylate (50.4).



50.3 **50.4**

DBU (0.10 mL, 0.67 mmol) was added dropwise to a stirred solution of alcohol **50.3** (0.117 g, 0.285 mmol) in Acetonitrile (5 mL). The mixture was heated at reflux (85 °C) for 5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 1:9 *t*-BuOMe-CH_2Cl_2, gave **50.4** (81.2 mg, 72%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2926, 1738, 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.89 (s, 9 H), 1.07-1.18 (m, 2 H), 1.27-1.35 (m, 1 H), 1.34 (dt, *J* = 0.6, 7.1 Hz, 3 H), 1.58-1.67 (m, 1 H), 1.87-1.93 (m, 1 H), 1.96-2.01 (m, 1 H), 2.08-2.21 (m, 4 H), 2.71-2.80 (m, 1 H), 2.94-3.03 (m, 1 H), 3.17 (tt, *J* = 3.1, 11.3 Hz, 1 H), 4.25-4.39 (m, 3 H), 4.51 (dd, *J* = 3.5, 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.31 (q), -5.30 (q), 14.3 (q), 18.3 (s), 21.4 (t), 24.0 (t), 24.7 (t), 26.0 (q), 29.5 (t), 29.6 (t), 33.7 (t), 59.0 (d), 60.6 (t), 63.6 (t), 70.5 (s), 120.2 (s), 162.8 (s), 166.7 (s), 184.3 (s); exact mass electrospray *m/z* calcd for $C_{21}H_{35}NNaO_4Si$ (M + Na) 416.2228, found 416.2227.

Methyl (4*R*,10a*S*)-4-[(*tert*-Butyldimethylsilyloxy)-methyl]-1,2,3,4,6,8,9,10-octahydro-6-oxocyclopenta-[*i*]indolizine-7-carboxylate (50.6).



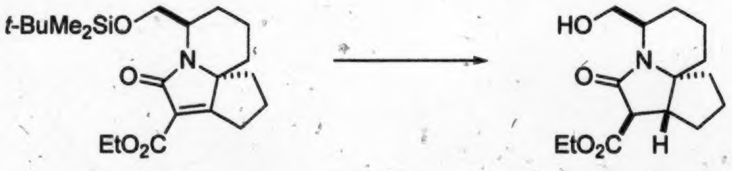
46.6 **50.6**

Et_3N (1.20 mL, 8.50 mmol), followed by methyl 3-chloro-3-oxopropionate (0.77 mL, 6.97 mmol) was added dropwise over ca. 10 min to a stirred and cooled (0 °C) solution of **46.6** (1.40 g, 4.71 mmol) in Acetonitrile (50 mL). The ice bath was removed and stirring was continued for 4 h. Saturated aqueous NH_4Cl (30 mL) was added to quench the reaction and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated to give the crude amide.

DBU (1.10 mL, 7.35 mmol) was added in one portion to a stirred solution of the above crude material in Acetonitrile (20 mL). The resulting mixture was heated at reflux (85 °C) for 10 h, and then cooled. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:9 *t*-BuOMe-CH_2Cl_2, gave **50.6** (1.48 g, 83%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2951, 1749, 1711, 1696

cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.90 (s, 9 H), 1.05-1.21 (m, 2 H), 1.26-1.37 (m, 1 H), 1.63 (tq, *J* = 3.4, 13.3 Hz, 1 H), 1.86-1.94 (m, 1 H), 2.00 (td, *J* = 3.0, 13.3 Hz, 1 H), 2.08-2.22 (m, 4 H), 2.71-2.82 (m, 1 H), 2.95-3.05 (m, 1 H), 3.15-3.23 (m, 1 H), 3.84 (s, 3 H), 4.36 (t, *J* = 10.2 Hz, 1 H), 4.50 (dd, *J* = 3.6, 10.4 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ -5.4 (q), -5.3 (q), 18.3 (s), 21.3 (t), 23.9 (t), 24.7 (t), 26.0 (q), 29.5 (t), 29.6 (t), 33.6 (t), 51.7 (q), 59.0 (d), 63.6 (t), 70.6 (s), 120.0 (s), 163.3 (s), 166.6 (s), 185.0 (s); exact mass (electrospray) *m/z* calcd for $C_{20}H_{33}NNaO_4Si$ (M + Na) 402.2071, found 402.2071.

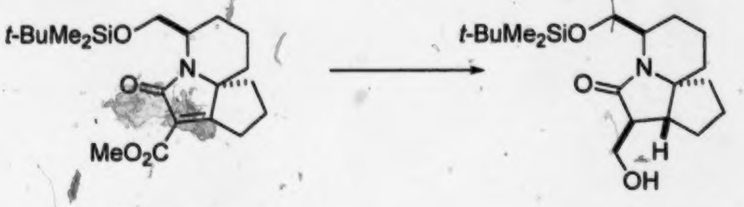
Ethyl (4*R*,7*R*,7a*R*,10a*S*)-Decahydro-4-(hydroxymethyl)-6-oxocyclopenta[*i*]indolizine-7-carboxylate (51.1).



50.4 **51.1**

Pd-C (10%, 10 mg) was added to a solution of **50.4** (32.9 mg, 0.08 mmol) in EtOAc (2 mL) contained in a Parr bottle, and the mixture was hydrogenated using a Parr shaker (50 psi) for 48 h. The mixture was then filtered through a Celite pad (1 x 1.5 cm), using CH$_2$Cl$_2$ (10 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave alcohol **51.1** (16.1 mg, 72%) as a colorless oil: FTIR (CH$_2$Cl$_2$ cast) 3381, 2939, 1734, 1664 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.31 (t, *J* = 7.1 Hz, 3 H), 1.43-1.55 (m, 2 H), 1.56-1.69 (m, 6 H), 1.76 (dd, J = 3.9, 13.2 Hz, 1 H), 1.79-1.91 (m, 2 H), 1.95-2.03 (m, 1 H), 2.54 (td, J = 4.5, 8.3 Hz, 1 H), 3.19 (dd, J = 0.9, 4.5 Hz, 1 H), 3.23-3.29 (m, 1 H), 3.83 (dd, J = 2.3, 12.6 Hz, 1 H), 3.94 (dd, J = 7.3, 12.7 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 4.66 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 21.6 (t), 24.8 (t), 27.9 (t), 33.3 (t), 35.3 (t), 37.1 (t), 47.0 (d), 56.9 (d), 58.8 (d), 61.7 (s), 63.1 (t), 73.1 (t), 168.6 (s), 170.7 (s); exact mass *m/z* calcd for $C_{15}H_{23}NO_4$ 281.1627, found 281.1630.

(4*R*,7*S*,7a*R*,10a*S*)-4-[(*tert*-Butyldimethylsilyloxy)-methyl]octahydro-7-(hydroxymethyl)cyclopenta[*i*]indolizin-6(7*H*)-one (52.1).

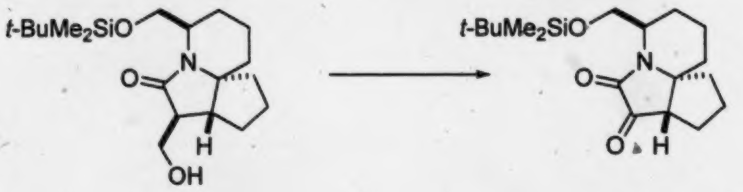


50.6 **52.1**

LiBH$_4$ (2.0 M in THF, 0.33 mL, 0.66 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **50.6** (100.0 mg, 0.26 mmol) in THF (8 mL) and MeOH (5 mL). The ice bath was left in place but not recharged and stirring was continued for 18 h. The mixture was quenched by addition of saturated aqueous NH$_4$Cl (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:2 EtOAc-hexane, gave alcohol **52.1** (81.5 mg, 87%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3391, 2938, 1652 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.24 (qd, *J* = 12.0, 4.0 Hz, 1 H), 1.44-1.75 (m, 7 H), 1.78-1.95 (m, 4 H), 2.02-2.09 (m, 1 H), 2.26-2.33 (m, 1 H), 3.14-3.23 (m, 1 H), 3.42 (s, 1 H), 3.68 (dd, *J* = 8.6, 10.5 Hz, 1 H), 3.76-3.84 (m, 1 H), 4.16 (t, *J* = 10.0 Hz, 1 H), 4.43 (dd, *J* = 4.0, 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.31 (q), -5.30 (q), 18.3 (s), 21.8 (t), 25.1 (t), 25.9 (q), 29.1 (t), 33.0 (t), 35.2 (t), 38.8 (t), 46.5 (d), 50.5 (d), 57.9 (d), 63.5 (t), 64.3 (t), 71.9 (s), 175.0 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{35}NNaO_3Si$ (M + Na) 376.2278, found 376.2279.

(4*R*,7a*R*,10a*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-octahydrocyclopenta[*i*]indolizin-6,7-dione (52.2).

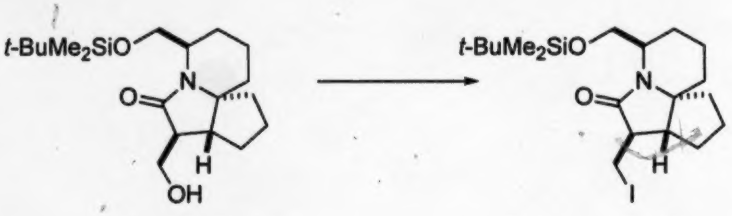


52.1 **52.2**

NMO (20.0 mg, 0.165 mmol), followed by TPAP (1.5 mg, 0.004 mmol) was added in one portion to a stirred solution of alcohol **52.1** (28.0 mg, 0.080 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 6 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 to 2:3 EtOAc-hexane, gave **52.2** (21.5 mg, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2956, 1767, 1709 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.14 (s, 3 H), 0.15 (s, 3 H), 0.75-0.91 (m, 2 H), 0.94-1.18 (m, 5 H), 1.00 (s, 9 H), 1.27-1.42 (m, 3 H), 1.51-1.59 (m, 1 H), 1.83 (dd, *J* = 3.6, 10.2 Hz, 1 H), 1.92-

1.99 (m, 1 H), 3.20-3.30 (m, 1 H), 4.44 (dd, J = 9.0, 10.3 Hz, 1 H), 4.84 (dd, J = 4.4, 10.3 Hz, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ -5.23 (q), -5.17 (q), 18.5 (s), 21.4 (t), 25.1 (t), 26.1 (q), 28.9 (t), 29.2 (t), 34.1 (t), 37.6 (t), 53.6 (d), 58.0 (d), 63.6 (t), 67.1 (s), 158.5 (s), 201.7 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{31}NNaO_3Si$ (M + Na) 360.1965, found 360.1963.

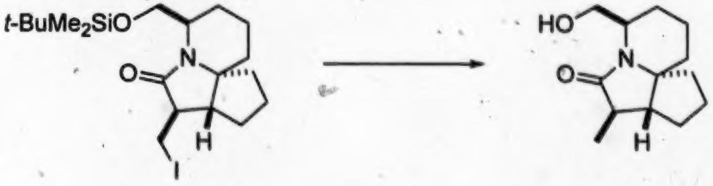
(4*R*,7*R*,7a*R*,10a*S*)-4-[(*tert*-Butyldimethylsilyloxy)-methyl]octahydro-7-(iodomethyl)cyclopenta[*i*]indolizin-6(7*H*)-one (53.1).



52.1 **53.1**

I_2 (0.291 g, 1.14 mmol) was added in one portion to a stirred and cooled (0 °C) solution of alcohol **52.1** (0.290 g, 0.82 mmol), Ph_3P (0.326 g, 1.23 mmol) and imidazole (0.112 g, 1.64 mmol) in CH_2Cl_2 (20 mL). The ice bath was removed and stirring was continued for 3 h. The reaction mixture was then filtered through a short pad of silica gel (2.5 x 3 cm), using 1:1 EtOAc-hexane (50 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:19 to 1:4 EtOAc-hexane, gave **53.1** (0.364 g, 96%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2953, 2884, 1686 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.09 (s, 6 H), 0.98 (s, 9 H), 1.00-1.08 (m, 2 H), 1.13-1.26 (m, 5 H), 1.35-1.54 (m, 4 H), 1.75-1.82 (m, 1 H), 1.97-2.05 (m, 2 H), 3.10-3.22 (m, 3 H), 4.39 (dd, J = 9.1, 10.3 Hz, 1 H), 4.85 (dd, J = 4.3, 10.3 Hz, 1 H); ^{13}C NMR (C_6D_6, 100.6 MHz) δ -5.2 (q), -5.1 (q), 10.1 (t), 18.5 (s), 22.0 (t), 25.2 (t), 26.2 (q), 29.4 (t), 33.2 (t), 35.3 (t), 38.6 (t), 50.4 (d), 51.6 (d), 58.1 (d), 64.1 (t), 70.0 (s), 170.9 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{35}INO_2Si$ (M + H) 464.1476, found 464.1479.

(4*R*,7*R*,7a*R*,10a*S*)-Octahydro-4-(hydroxymethyl)-7-methylcyclopenta[*i*]indolizin-6(7*H*)-one (53.2).

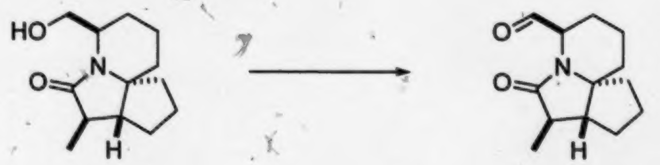


53.1 **53.2**

Bu_3SnH (0.43 mL, 1.55 mmol) and AIBN (10 mg) were added in one portion to a stirred and refluxing (oil bath at 85 °C) solution of iodide **53.1** (0.359 g, 0.78 mmol) in PhH (20 mL). Stirring was continued for 4 h at 85 °C and the mixture was then cooled to room temperature. The solvent was concentrated, and the residue was dissolved in THF (5 mL). TBAF (1.0 M in THF, 3.0 mL, 3.00 mmol) was added with stirring in one portion to the above solution. Stirring was continued for 10 h and the solvent was concentrated. The residue was diluted with Et_2O (50 mL) and then filtered through a Celite pad (2.5 x 1 cm), using Et_2O (50 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 25 cm), using 1:1 EtOAc-hexane, gave alcohol **53.2** (172 mg, 99%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3350, 2935, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, J = 7.4 Hz, 3 H), 1.42-1.74

(m, 9 H), 1.78-1.92 (m, 4 H), 2.15-2.23 (m, 1 H), 3.18-3.26 (m, 1 H), 3.85-3.92 (m, 2 H), 5.14 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.7 (q), 21.6 (t), 24.8 (t), 28.3 (t), 32.6 (t), 35.1 (t), 38.8 (t), 44.6 (d), 51.9 (d), 58.3 (d), 63.4 (t), 72.9 (s), 176.5 (s); exact mass *m/z* calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1571.

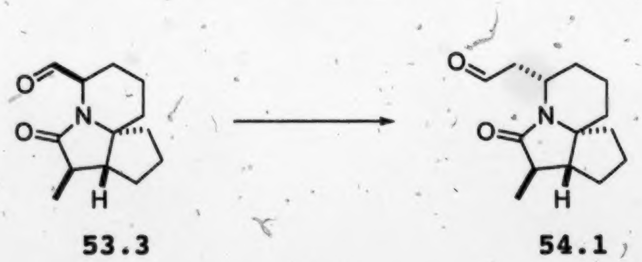
(4*R*,7*R*,7a*R*,10a*S*)-Decahydro-7-methyl-6-oxocyclopenta[*i*]indolizin-4-carbaldehyde (53.3).



53.2 **53.3**

Dess-Martin periodinane (0.270 g, 0.62 mmol) was added in one portion to a stirred solution of alcohol **53.2** (0.104 g, 0.45 mmol) in CH_2Cl_2 (15 mL). Stirring was continued for 1 h and the mixture was filtered through a Celite pad (2 x 1 cm), using CH_2Cl_2 (20 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 20 cm), using 1:4 to 4:1 EtOAc-hexane, gave aldehyde **53.3** (92 mg, 93%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2936, 1726, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (d, *J* = 7.4 Hz, 3 H), 1.44-1.92 (m, 12 H), 1.97-2.02 (m, 1 H), 2.14-2.20 (m, 1 H), 3.49-3.55 (m, 1 H), 9.86 (d, *J* = 2.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.0 (q), 20.7 (t), 24.8 (t), 24.9 (t), 32.0 (t), 34.7 (t), 37.9 (t), 42.8 (d), 53.1 (d), 60.9 (d), 69.3 (s), 176.4 (s), 195.6 (d); exact mass *m/z* calcd for $C_{13}H_{19}NO_2$ 221.1415, found 221.1410.

2-[(4*S*,7*R*,7a*R*,10a*S*)-Decahydro-7-methyl-6-oxocyclopenta[*i*]indolizin-4-yl]acetaldehyde (54.1).

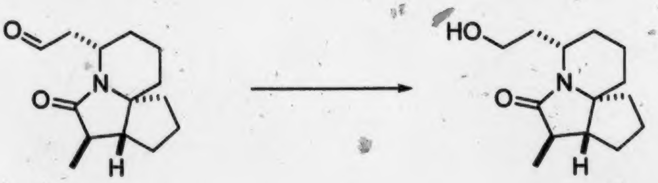


53.3 **54.1**

KHMDS (0.5 M in PhMe, 1.6 mL, 0.80 mmol) was added dropwise to a stirred solution of $Ph_3PCH_2(OCH_3)Cl$ (0.344 g, 0.90 mmol) in PhMe (5 mL). Stirring was continued for 60 min, and aldehyde **53.3** (50 mg, 0.23 mmol) in PhMe (5 mL) was added dropwise over ca. 2 min. Stirring at room temperature was continued for 10 h and the reaction mixture was quenched by addition of MeOH (3 mL), and filtered through a short pad of silica gel (2 x 3 cm), using EtOAc (30 mL) as a rinse. The solvent was concentrated and the residue was diluted with hydrochloric acid (1 N, 3 mL) and THF (6 mL). The resulting mixture was stirred at room temperature for 4 h and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:2 acetone-hexane, gave aldehyde **54.1** (39 mg, 73%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2935, 2868, 1725, 1679, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 7.3 Hz, 3 H), 1.22-1.33 (m, 1 H), 1.40-1.49 (m, 1 H), 1.60-1.88 (m, 10 H), 1.89-1.98 (m, 1 H), 2.10-2.18 (m, 1 H), 2.54-2.74 (m, 2 H), 4.90-4.98 (m, 1 H), 9.71 (dd, J = 1.8, 3.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.2 (t), 17.3 (q), 25.5 (t), 28.3 (t), 30.8 (t), 37.7 (t), 38.1 (t), 42.9 (d), 43.6 (d), 47.3 (t), 54.0

(d), 68.3 (s), 176.0 (s), 201.0 (d); exact mass (electrospray) *m/z* calcd for $C_{14}H_{21}NNaO_2$ (M + Na) 258.1465, found 258.1466.

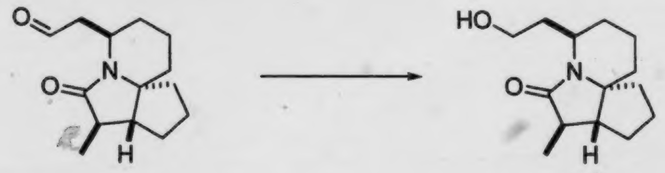
(4*S*,7*R*,7a*R*,10a*S*)-Octahydro-4-(2-hydroxyethyl)-7-methylcyclopenta[*i*]indolizin-6(7*H*)-one (54.2).



54.1 **54.2**

$NaBH_4$ (30 mg, 0.75 mmol) was added in one portion to a stirred and cooled (0 °C) solution of aldehyde **54.1** (39 mg, 0.17 mmol) in MeOH (6 mL). The ice bath was left in place but not recharged and stirring was continued for 4 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:2 acetone-hexane, gave alcohol **54.2** (26 mg, 66%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3400, 2937, 1677, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (d, *J* = 7.2 Hz, 3 H), 1.31-1.37 (m, 1 H), 1.50-1.82 (m, 12 H), 1.87-1.93 (m, 2 H), 2.24 (quintet, *J* = 7.2 Hz, 1 H), 3.37 (tt, *J* = 3.2, 12.1 Hz, 1 H), 3.60-3.67 (m, 1 H), 4.20 (dd, *J* = 3.8, 10.9 Hz, 1 H), 4.38-4.45 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 17.3 (q), 17.5 (t), 25.3 (t), 28.8 (t), 30.3 (t), 35.4 (t), 37.3 (t), 38.3 (t), 43.7 (d), 44.7 (d), 54.2 (d), 58.7 (t), 69.0 (s), 177.6 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{23}NNaO_2$ (M + Na) 260.1621, found 260.1624.

(4*R*,7*R*,7a*R*,10a*S*)-Octahydro-4-(2-hydroxyethyl)-7-methylcyclopenta[*i*]indolizin-6(7*H*)-one (54.4).



54.3 **54.4**

$LiBH_4$ (2.0 M in THF, 0.1 mL, 0.20 mmol) was added dropwise over ca. 1 min to a stirred and cooled (0 °C) solution of aldehyde **54.3** (10 mg, 0.043 mmol) in THF (2 mL) and MeOH (1 mL). The ice bath was left in place but not recharged and stirring was continued for 4 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:3 acetone-hexane, gave alcohol **54.4** (9 mg, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3409, 2931, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, *J* = 7.5 Hz, 3 H), 1.42-1.54 (m, 3 H), 1.58-1.73 (m, 6 H), 1.75-1.83 (m, 3 H), 1.88-1.98 (m, 3 H), 2.14-2.22 (m, 1 H), 2.72-2.81 (m, 1 H), 3.35-3.44 (m, 1 H), 3.69-3.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.5 (q), 21.7 (t), 25.1 (t), 31.7 (t), 32.5 (t), 35.1 (t), 35.6 (t), 38.1 (t), 44.7 (d), 51.7 (d), 53.3 (d), 60.8 (t), 72.0 (s), 177.0 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{23}NNaO_2$ (M + Na) 260.1621, found 260.1623.

IV References and Notes

1 Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867-3870.

2 (a) Springer, T. A. *Cell* **1994**, *76*, 301-314. (b) Carlos, T. M.; Harlan, J. M. *Blood* **1994**, *84*, 2068-2101.

3 Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871-3874.

4 ven den Bosch, H. *Biochim. Biophys. Acta* **1980**, *604*, 191-246.

5 Kim, D. K.; Kudo, I.; Fujimori, Y.; Mizushima, H.; Masuda, M.; Kikuchi, R.; Ikizawa, K.; Inoue, K. *J. Biochem.* **1990**, *108*, 903-906.

6 Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861-862.

7 Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4453-4456.

8 (a) Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513-6516. (b) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3542-3545. (c) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344-2351.

9 Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4450-4452.

10 Lee, S.; Zhao, Z. *Org. Lett.* **1999**, *1*, 681-683.

11 Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921-7924.

12 Shindo, M.; Fukuda, Y. I.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929-932.

13 Yokota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 875-885.

14 Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583-3586.

15 Hayakawa, I.; Arimoto, H.; Uemura, D. *Heterocycles* **2003**, *59*, 441-444.

16 Hayakawa, I.; Arimoto, H.; Uemura, D. *Chem. Commun.* **2004**, 1222-1223.

17 White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413-415.

18 Takasu, K.; Ohsato, H.; Ihara, M. *Org. Lett.* **2003**, *5*, 3017-3020.

19 Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2004**, *6*, 965-968.

20 Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3249-3252.

21 Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503-8507.

22 Goldspink, N. J.; Simpkins, N. S.; Beckmann, M. *Synlett* **1999**, 1292-1294.

23 Dieck, H. T.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 694-701.

24 Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391-3394.

25 Chrystal, E. J. T.; Couper, L.; Robins, D. J. *Tetrahedron* **1995**, *51*, 10241-10252.

26 Chênevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332-3341.

27 Swarbrick, M. E.; Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1999**, *64*, 1993-2002.

28 HPLC conditions: ChiralPak AS column (10 μm, 4.6 x 250 mm); sample injection (10 μL, 1 mg/mL of 10% EtOH/hexane); 5% EtOH/hexane as eluent; flow speed at 1.0 mL/min; PDA detector (190-320 nm); integrated @ 205 nm.

29 Yu, M.; Clive, D. L. J.; Yeh, V. S. C.; Kang, S.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 2879-2881.

30 Personal communication from Professor N. S. Simpkins.

31 These studies were done by Vince Yeh.

32 Some reaction conditions shown in Scheme 23 (from compound **23.4** to **23.10**) were developed by Vince Yeh during his studies.

33 Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048-5050.

34 Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526-5528.

35 Cf. Evans, P. A.; Holmes, A. B.; McGeary, R. P.; Nadin, A.; Russell, K. *J. Chem. Soc., Perkin Trans. 1* **1996**, 123-138.

36 Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017-3020.

37 (a) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650-657. (b) Ireland, R. E.; Wipf, P.; Xiang, J. *J. Org. Chem.* **1991**, *56*, 3572-3582.

38 Clive, D. L. J.; Magnuson, S. R.; Manning, H. W.; Mayhew, D. L. *J. Org. Chem.* **1996**, *61*, 2095-2108.

39 McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1213-1215.

40 Coe, D. M.; Perciaccante, R.; Procopiou, P. A. *Org. Biomol. Chem.* **2003**, *1*, 1106-1111.

41 Wakita, H.; Yoshiwara, H.; Nishiyama, H.; Nagase, H. *Heterocycles* **2000**, *53*, 1085-1110.

42 Manchand, P. S.; Yinikouros, G. P.; Belica, P. S.; Mandan, P. *J. Org. Chem.* **1995**, *60*, 6574-6581.

43 Ikede, M.; Matsubayashi, K.; Imoto, T.; Kitao, K.; Ishibashi, H.; Sato, T. *Heterocycles* **1994**, *38*, 1237-1240.

44 Clarke, T. C.; Wendling, L. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 2740-2750.

45 Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903-10908.

46 Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478-479.

47 Cf. Ph. D. Thesis, Yeh, V. S. C., University of Alberta, 2001: an *N*-benzylated diene failed to undergo ring closing metathesis with the first generation Grubbs catalyst. However, the second generation catalyst was not tried.

48 (a) Yu, J.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727-2730. (b) Yu, J.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232-3233.

49 Mihelich, E.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135-4137.

50 Biggs, D. C. H.; Lesimple, P. *Synthesis* **1992**, 277-278.

51 Brown, R. F. C.; Coulston, K. J.; Eastwood, F. W.; Gatehouse, B. M.; Guddatt, L. W. *Aust. J. Chem.* **1984**, *37*, 2509-2524.

52 (a) Lermer, L.; Neeland, E. G.; Ounsworth, J. P.; Sims, R. J.; Tischler, S. A.; Weiler, L. *Can. J. Chem.* **1992**, *70*, 1427-1445. (b) Eberlein, T. H.;

West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479-3482.

53 Jacobus, J.; Leibner, J. E. *J. Org. Chem.* **1979**, *44*, 449-450.